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(54) Title: METHODS, COMPOSITIONS, AND PREPARATIONS FOR DELIVERY OF IMMUNE RESPONSE MODIFIERS

(57) Abstract: A soluble IRM-polymer complex, preparations thereof, and methods of use, wherein the soluble IRM-polymer com-  
plex includes one or more IRM compounds attached (e.g., covalently attached) to a polymer (e.g., an alkylene oxide-containing  
polymer).

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METHODS, COMPOSITIONS, AND PREPARATIONS FOR DELIVERY OF  
IMMUNE RESPONSE MODIFIERS

CROSS-REFERENCE TO RELATED APPLICATIONS

The present application claims priority to U.S. Provisional Patent Application  
Serial No. 60/560862, filed on April 9, 2004, and to U.S. Provisional Patent Application  
Serial No. 60/617196, filed on October 8, 2004, both of which are incorporated herein by  
reference.

BACKGROUND

There has been a major effort in recent years, with significant successes, to  
discover new drug compounds that act by stimulating certain key aspects of the immune  
system, as well as by suppressing certain other aspects (see, e.g., U.S. Pat. Nos. 6,039,969  
and 6,200,592). These compounds, sometimes referred to as immune response modifiers  
(IRMs), appear to act through basic immune system mechanisms known as toll-like  
receptors to induce selected cytokine biosynthesis and may be used to treat a wide variety  
of diseases and conditions. For example, certain IRMs may be useful for treating viral  
diseases (e.g., human papilloma virus, hepatitis, herpes), neoplasias (e.g., basal cell  
carcinoma, squamous cell carcinoma, actinic keratosis, melanoma), and TH2-mediated  
diseases (e.g., asthma, allergic rhinitis, atopic dermatitis), and are also useful as vaccine  
adjuvants. Unlike many conventional anti-viral or anti-tumor compounds, the primary  
mechanism of action for IRMs is indirect, by stimulating the immune system to recognize  
and take appropriate action against a pathogen.

Many of the IRM compounds are small organic molecule imidazoquinoline amine  
derivatives (see, e.g., U.S. Pat. No. 4,689,338), but a number of other compound classes  
are now known as well (see, e.g., U.S. Pat. Nos. 5,446,153; 6,194,425; and 6,110,929) and  
more are still being discovered. Other IRMs have higher molecular weights, such as  
oligonucleotides, including CpGs (see, e.g., U.S. Pat. No. 6,194,388). In view of the great  
therapeutic potential for IRMs, and despite the important work that has already been done,

there is a substantial ongoing need for new means of controlling the delivery and activity of IRMs in order to expand their uses and therapeutic benefits.

### SUMMARY

5           In some circumstances it is desirable to avoid broad systemic activity by immune response modifier (IRM) compounds (described *infra*), and the effectiveness of many IRMs delivered systemically may be enhanced through targeting and preferential uptake of the IRM by particular biological tissues or organs. This approach can be used to prevent, or at least reduce the occurrence of, the systemic activity of the IRM. In other words, even  
10           though the IRM can be conveniently delivered systemically, if desired, its biologic activity is concentrated at particular locations where desired.

          This can be accomplished by attaching (preferably covalently attaching) one or more IRMs to an organic polymer to form a soluble complex (herein referred to as a soluble IRM-polymer complex). That is, a soluble IRM-polymer complex of the present  
15           invention is of a size and chemical nature to allow preferential deposition in certain tissues (e.g., particular tissue types and/or localized tissue regions) such as solid tumors, lymph tissue, reticuloendothelial system, bone marrow, mucosal tissue, etc.

          Typically, the polymer of the soluble IRM-polymer complex is also soluble prior to attachment of one or more IRMs. Preferably, the polymer (i.e., polymer carrier  
20           material) includes alkylene oxide (e.g., ethylene oxide) moieties. Such polymers are referred to herein as "alkylene oxide-containing polymers."

          In this context, in certain embodiments, "soluble" refers to a polymer IRM-complex (and/or, typically, the polymer prior to attachment of the one or more IRMs) having a solubility of at least 1 microgram per milliliter in water under physiological  
25           conditions (i.e., pH 7.4 and 37°C). In certain embodiments, the polymer-IRM complex (and/or the polymer prior to attachment of the one or more IRMs) has a solubility of at least 0.1 microgram per milliliter in water under physiological conditions. In certain  
          embodiments, the polymer-IRM complex (and/or the polymer prior to attachment of the one or more IRMs) has a solubility of at least 0.1 and less than 1 microgram per milliliter  
30           in water under physiological conditions.

          The IRM can be biologically active while attached (preferably, covalently attached) to the polymer (preferably, polyalkylene oxide-containing polymer), although

this is not a necessary requirement of the invention. For example, the IRM may be "inactive" due to masking of its activity by folding of the polymer carrier material around the IRM or due to the IRM-polymer linkage to a position on the IRM required for IRM activity. Once the soluble IRM-polymer complex has reached a targeted site, the IRM can  
5 detach from the polymer carrier material (preferably, polyalkylene oxide-containing carrier material) (e.g., through biodegradation of the polymer-IRM bond or unfolding of the polymer carrier material), thereby resulting in availability or activation of the IRM. Other mechanisms of activation of the IRM may also occur once the soluble IRM-complex has reached a targeted site.

10 Accordingly, the invention includes a method of providing an IRM compound to a targeted tissue region (e.g., a localized tissue region and/or tissue type (i.e., cell type)) using a soluble IRM-polymer complex disclosed herein. The IRM localized tissue region may be, e.g., a cancer, a viral infected lesion, or organ, or vaccination site. It may be a solid tumor, lymph tissue, reticuloendothelial system, bone marrow, mucosal tissue, etc.  
15 The localized tissue region may be, e.g., a breast cancer tumor, stomach cancer tumor, lung cancer tumor, head or neck cancer tumor, colorectal cancer tumor, renal cell carcinoma tumor, pancreatic cancer tumor, basal cell carcinoma tumor, pancreatic cancer tumor, cervical cancer tumor, melanoma cancer tumor, prostate cancer tumor, ovarian cancer tumor, or bladder cancer tumor.

20 The IRM may be an agonist of at least one TLR selected from the group consisting of TLR7, TLR8, and combinations thereof. The IRM may be a selective TLR agonist of TLR 7, or TLR 8, or an agonist of both TLR 7 and 8. The IRM may preferably be a small molecule immune response modifier, for example, comprising a 2-aminopyridine fused to a five-membered nitrogen-containing heterocyclic ring.

25 In one embodiment, the present invention provides a method of delivering one or more IRM compounds to a tissue in a subject, the method involves administering (preferably, systemically administering) an IRM preparation to the subject, wherein the IRM preparation includes a soluble IRM-polymer complex including one or more IRM compounds attached to a polymer.

30 Herein, in certain embodiments, a soluble IRM-polymer complex is one that has a solubility in water of at least 1 microgram per milliliter under physiological conditions. In certain embodiments, the IRM-polymer complex has a solubility of at least 0.1 microgram

per milliliter in water under physiological conditions, and in certain embodiments, a solubility of at least 0.1 and less than 1 microgram per milliliter in water under physiological conditions. In certain embodiments, the IRM-polymer complex has a solubility in water of at least 10 micrograms per milliliter under physiological conditions.

5 In certain embodiments, the IRM-polymer complex has a solubility in water of at least 100 micrograms per milliliter under physiological conditions.

Preferably, the one or more IRM compounds are covalently attached to the polymer. Preferably, the polymer is soluble prior to attachment of the one or more IRM compounds. That is, in certain embodiments, the polymer prior to attachment of the one  
10 or more IRM compounds preferably has a solubility in water of at least 1 microgram per milliliter under physiological conditions. In certain embodiments, the polymer prior to attachment of the one or more IRM compounds has a solubility of at least 0.1 microgram per milliliter in water under physiological conditions, and in certain embodiments, a solubility of at least 0.1 and less than 1 microgram per milliliter in water under  
15 physiological conditions. In certain embodiments, the polymer prior to attachment of the one or more IRM compounds has a solubility in water of at least 10 micrograms per milliliter under physiological conditions. In certain embodiments, the polymer prior to attachment of the one or more IRM compounds has a solubility in water of at least 100 micrograms per milliliter under physiological conditions.

20 The polymer can be selected from the group consisting of poly(alkylene glycols), poly(olefinic alcohols), polyvinylpyrrolidones, poly(hydroxyalkylmethacrylamides), poly(hydroxyalkylmethacrylates), polyvinyl alcohols, polyoxazolines, poly(acrylic acids), polyacrylamides, polyglutamates, polylysines, polysaccharides, and combinations thereof. In certain embodiments, the polymer includes alkylene oxide moieties.

25 In another embodiment, the present invention provides a method of delivering one or more IRM compounds to a tissue in a subject, wherein the method includes administering (preferably, systemically administering) an IRM preparation to the subject, wherein the IRM preparation includes a soluble IRM-polymer complex including one or more IRM compounds attached to a soluble polymer having alkylene oxide moieties,  
30 wherein the IRM-polymer complex has a molecular weight of 1 kDa to 500 kDa, and in certain embodiments 1 kDa to 200 kDa.

The polymer (and/or the IRM-polymer complex) typically can have a molecular weight of at least 1 kDa, or at least 20 kDa, or at least 30 kDa. The polymer (and/or the IRM-polymer complex) typically can have a molecular weight of no greater than 500 kDa, or no greater than 200 kDa, or no greater than 100 kDa, or no greater than 50 kDa. The  
5 polymer (and/or the IRM-polymer complex) can have a molecular weight of 1 kDa to 200 kDa, or 1 kDa to 100 kDa, or 1 kDa to 50 kDa. In certain embodiments, the polymer (and/or the IRM-polymer complex) can have a molecular weight of 1 kDa to 500 kDa, or 20 kDa to 200 kDa, or 30 kDa to 100 kDa.

The present invention also provides a soluble IRM-polymer complex that includes  
10 one or more IRM compounds attached to a polymer. In certain embodiments, the polymer prior to attachment of the one or more IRM compounds has a solubility in water of at least 1 microgram per milliliter under physiological conditions. In certain embodiments, the polymer prior to attachment of the one or more IRM compounds has a solubility of at least  
15 0.1 microgram per milliliter in water under physiological conditions, and in certain embodiments, a solubility of at least 0.1 and less than 1 microgram per milliliter in water under physiological conditions. In certain embodiments the polymer includes alkylene oxide-containing moieties.

IRM preparations are also provided that include one or more soluble IRM-polymer complexes as defined herein. Such preparations can also include one or more additional  
20 active agents, which may or may not be attached to the polymer. For example, a preparation can include one or more IRM compounds that are not attached to the polymer.

Herein, "polymer" is used to encompass homopolymers and copolymers, "copolymer" is used to encompass polymers prepared from two or more different monomers (e.g., terpolymers, tetrapolymers, etc.).

25 The term "comprises" and variations thereof do not have a limiting meaning where these terms appear in the description and claims.

As used herein, "a," "an," "the," "at least one," and "one or more" are used interchangeably. Thus, for example, a complex that comprises "an" IRM can be interpreted to mean that the complex includes "one or more" IRMs. Similarly, a  
30 composition comprising "a" complex can be interpreted to mean that the composition includes "one or more" complexes.

As used herein, "treating" a condition or a subject includes therapeutic, prophylactic, and diagnostic treatments.

Also herein, the recitations of numerical ranges by endpoints include all numbers subsumed within that range (e.g., 1 to 5 includes 1, 1.5, 2, 2.75, 3, 3.80, 4, 5, etc.).

5       The above summary of the present invention is not intended to describe each disclosed embodiment or every implementation of the present invention. The description that follows more particularly exemplifies illustrative embodiments. In several places throughout the application, guidance is provided through lists of examples, which examples can be used individually and in various combinations. In each instance, the  
10       recited list serves only as a representative group and should not be interpreted as an exclusive list.

#### DETAILED DESCRIPTION OF ILLUSTRATIVE EMBODIMENTS OF THE INVENTION

15       The present invention is directed to methods, complexes, and preparations (i.e., compositions or formulations) of immune response modifiers (IRMs) that can be preferentially targeted to a localized tissue region and/or tissue type and/or provide locally (or systemically) active IRM compounds for an extended period of time. Such complexes include a polymer carrier material having one or more IRM compounds attached thereto.

20       A soluble IRM-polymer complex of the present invention is of a size and chemical nature to allow preferential deposition in certain tissues (e.g., particular tissue types and/or localized tissue regions) such as solid tumors, lymph tissue, reticuloendothelial system, bone marrow, mucosal tissue, etc. Such IRM-polymer complexes are soluble in water (i.e., for certain embodiments at least 1 microgram per milliliter, and for certain  
25       embodiments at least 0.1 microgram per milliliter) under physiological conditions. Due to the solubility of the IRM-polymer complex, one advantage of the present invention is that the circulatory system can be used to quickly distribute the complex throughout the body. Also, a clear or semi-clear solution of the soluble IRM-polymer complex may be more easily administered to a patient than a formulation that includes particulates, emulsions, or  
30       other constructs.

Another advantage can be described in terms of the IRM half-life. To illustrate, if a conventional solution formulation of a given IRM compound is injected systemically,

the IRM compound has a short half-life and is quickly removed via renal excretion. By contrast, if a soluble IRM-polymer complex such as those described herein is injected systemically the large molecular weight of the IRM-polymer complex overcomes renal excretion, increasing the half-life of the IRM.

5           The present invention thus provides active IRMs accumulated within a localized tissue region and/or tissue type in an amount greater than and/or for a time longer than a comparable concentration of the IRM in a conventional solution. For example, the tissue concentration for the IRM when administered as an IRM-polymer complex is preferably at least 50% greater than the localized tissue concentration for an uncomplexed IRM when  
10 administered in a similar manner. For example, the residence half-life for the IRM when administered as an IRM-polymer complex is preferably at least 50% greater than the residence half life of an uncomplexed IRM.

          Polymers for use in the soluble IRM-polymer complexes may be sufficiently flexible in water to mask or hide an active IRM from the immune system preventing or  
15 reducing a systemic response and local response at the administration site (typically, by preventing or reducing immune cell receptors from attaching to the IRM). It is believed that unfolding and/or biodegradation of the polymer will make the IRM available for stimulating an immune response. Alternatively, the polymer can be less flexible so that it does not envelop the IRM, in which case, depending on the attachment site of the polymer  
20 on the IRM, the IRM may be active while it is still attached to the polymer.

          The flexibility and solubility of preferred IRM-polymer complexes of the present invention are believed to allow for temporal fluctuations in polymer conformation, thereby preventing, or reducing the occurrence of immune cell receptors from latching on to a fixed molecular structure. Although not intending to be limiting, this is believed to  
25 contribute to the complex remaining inactive until the target site is reached, thereby potentially reducing systemic side effects of IRMs.

          Furthermore, the enhanced permeability and retention (EPR) effect in tumor vasculature is believed to facilitate extravasation of the IRM-polymer complex selectively at the tumor site and allow it to accumulate therein (see, e.g., Hiroshi Maeda, *Advanced*  
30 *Drug Delivery Reviews*, 6(2): 181-202, (1991)).

          Additionally, the IRM-polymer complex can be designed, e.g., by attaching a particular antibody to the complex, to target and bind to tumor antigens present at the

tumor or in the circulatory system, thereby inducing a more potent immune response. In this fashion, the IRM-polymer-antibody complex could induce an immune response targeted to the tumor antigen.

Also, accumulation of a soluble IRM-polymer complex in the targeted tissue may  
5 cause inflammation that could attract effector and/or memory T cells into the area.

Another advantage of the present invention is to 'protect' the IRM from immune cells and thus avoid or reduce the generation of antibodies against the IRM and eliminate potential allergic responses to the IRM pharmacophore.

The benefits of the present invention in terms of improved targeting of the immune  
10 system, with reduced systemic activity, can be accomplished with many different soluble IRM-polymer complexes, optionally with other active agents, and can be targeted to various localized tissue regions and/or tissue types for a wide range of treatments.

#### *Soluble IRM-Polymer Complexes and Preparations Thereof*

15 As described above, a soluble IRM-polymer complex (and preparations and compositions thereof) can provide active IRM compound, after delivery (preferably systemic delivery), for an extended period to a localized tissue region and/or tissue type, while reducing overall systemic activity of the IRM.

This can be accomplished by attaching (preferably covalently attaching) one or  
20 more IRMs to an organic polymer to form a soluble complex (herein referred to as a soluble IRM-polymer complex). That is, a soluble IRM-polymer complex of the present invention is of a size and chemical nature to allow preferential deposition in tissues (e.g., particular tissue types or localized tissue regions) such as solid tumors. This can occur as a result of the tissue's increased vascular permeability, for example, to soluble IRM-  
25 polymer complexes of the present invention, and the reduced lymphatic drainage of tumor tissues.

Typically, the polymer of the soluble IRM-polymer complex is also soluble prior to attachment of one or more IRMs. Preferably, the polymer (i.e., polymer carrier material) includes alkylene oxide (e.g., ethylene oxide) moieties. Such polymers are  
30 referred to herein as "alkylene oxide-containing polymers."

In this context, in certain embodiments, "soluble" refers to an IRM-polymer complex having a solubility of at least 1 microgram per milliliter in water under

physiological conditions (i.e., pH 7.4 and 37°C). Typically, prior to attachment, the polymer of the IRM-polymer complex has a solubility of at least 1 microgram per milliliter in water under physiological conditions (i.e., pH 7.4 and 37°C). In certain embodiments, however, an IRM-polymer complex has a solubility of at least 0.1  
5 microgram per milliliter in water under physiological conditions (i.e., pH 7.4 and 37°C). In certain embodiments, prior to attachment, the polymer of the IRM-polymer complex has a solubility of at least 0.1 microgram per milliliter in water under physiological conditions (i.e., pH 7.4 and 37°C). In certain embodiments, an IRM-polymer complex, and/or the polymer prior to attachment of an IRM, has a solubility of at least 0.1 and less  
10 than 1 microgram per milliliter in water under physiological conditions.

For certain embodiments, the IRM-polymer complex, and/or the polymer prior to attachment of an IRM, has a solubility of at least 10 micrograms per milliliter in water under physiological conditions. For certain embodiments, the IRM-polymer complex, and/or the polymer prior to attachment of an IRM, has a solubility of at least 100  
15 micrograms per milliliter in water under physiological conditions.

As long as the IRM-polymer complex is sufficiently soluble, the complex (and the polymer prior to attachment of one or more IRMs) can be of a wide variety of molecular weights. Preferably, the complex (and/or the polymer prior to attachment of one or more IRMs) has a molecular weight of at least 1 kilodalton (kDa). More preferably, the  
20 complex (and/or the polymer prior to attachment of one or more IRMs) has a molecular weight of at least 20 kDa. Even more preferably, the complex (and/or the polymer prior to attachment of one or more IRMs) has a molecular weight of at least 30 kDa. Preferably, the complex (and/or the polymer prior to attachment of one or more IRMs) has a molecular weight of no greater than 500 kilodaltons (kDa). More preferably, the complex  
25 (and/or the polymer prior to attachment of one or more IRMs) has a molecular weight of no greater than 200 kDa. Even more preferably, the complex (and/or the polymer prior to attachment of one or more IRMs) has a molecular weight of no greater than 100 kDa, and often no greater than 50 kDa.

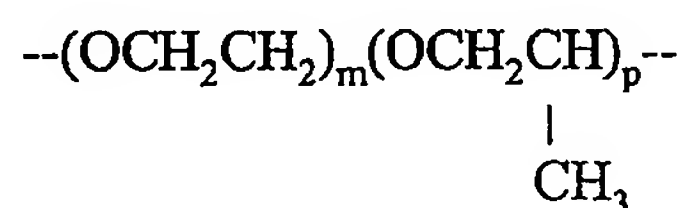
Suitable polymers for attachment (preferably covalent attachment) to an IRM  
30 include poly(alkylene glycols) (i.e., polyalkylene oxides) such as poly(oxyethylated polyols), poly(olefinic alcohols), polyester polyols, polyvinylpyrrolidones, poly(hydroxyalkylmethacrylamides), poly(hydroxyalkylmethacrylates), polyvinyl

alcohols, polyoxazolines (e.g., polyethyloxazoline), poly(acrylic acids) (typically, those that are not crosslinked), polyacrylamides, polyglutamates, polylysines, polysaccharides, and combinations thereof (e.g., copolymers, terpolymers, etc., and mixtures thereof).

Preferably, suitable polymers are those within these classes that are soluble (i.e., have a solubility of at least 1 microgram per milliliter in water under physiological conditions, and in certain embodiments, have a solubility of at least 0.1 microgram per milliliter in water under physiological conditions). Particularly suitable polymers within these classes of polymers are those that have a solubility of at least 10 micrograms per milliliter in water under physiological conditions, and often at least 100 micrograms per milliliter in water under physiological conditions.

Examples of preferred aqueous soluble polymers include polyvinyl alcohols, polyacrylamides, polyalkylene oxides (e.g., polyethylene oxide), poly(hydroxyalkylmethacrylamides) (e.g., poly N-(2-hydroxypropyl) methacrylamide), polyglutamates, polylysines, polysaccharides (e.g., cellulose (e.g., carboxymethyl cellulose, hydroxypropylmethyl cellulose), starch, dextran amylose, glycogen, chitin, etc.), and combinations thereof (e.g., copolymers and mixtures thereof). Particularly preferred polymers include alkylene oxide (preferably, ethylene oxide) moieties.

A preferred class of aqueous soluble polymers include poly(alkylene oxide) polymers that include C<sub>2</sub>-C<sub>4</sub> alkylene oxide moieties, particularly the following alkylene oxide moieties:



wherein m is at least 2 (and more preferably, at least 25) and p is 0 to 9,000 (and, in certain embodiments 0 to 5,000, in certain embodiments, 0 to 1,000, and in certain embodiments, 0 to 50). In this representation, the isopropylene oxide groups (the "p" groups) and the ethylene oxide groups (the "m" groups) can be arranged in a reversed, alternating, random, or block configuration. In any one polymer, m is preferably at least 4 (more preferably, at least 25, even more preferably, at least 450, and even more preferably, at least 700). Preferably, m is no greater than 12,000 (more preferably, no greater than 5000, even more preferably, no greater than 2,500, even more preferably, no greater than

1,000, even more preferably, no greater than 115, even more preferably, no greater than 45, and even more preferably, no greater than 25). Preferably, p is 0.

Commercially available polyethylene glycols (PEG) include those having backbones of the formulas  $\text{HO}-(\text{CH}_2\text{CH}_2\text{O})_n-\text{CH}_2\text{CH}_2-\text{OH}$  (PEG) and  $\text{CH}_3\text{O}-(\text{CH}_2\text{CH}_2)_n-\text{CH}_2\text{CH}_2-\text{OH}$  (mPEG), which are modified for attachment of one or more IRMs. Specific materials that are commercially available include, but are not limited to, ACRL-PEG-NHS, Biotin-PEG-NHS, Boc-Protected Amine, Fluorescein-PEG-NHS, Fmoc-Protected Amine, NHS-PEG-Maleimide, NHS-PEG-Vinylsulfone, mPEG-Acetaldehyde Diethyl Acetal, mPEG-Benzotriazole Carbonate, mPEG-ButyrALD, mPEG-Double Esters, mPEG-DSPE, mPEG-Forked Maleimide, mPEG-Maleimide, mPEG-NH<sub>2</sub>, mPEG-Succinimidyl Butanoate, mPEG-Succinimidyl Propionate, mPEG-Thioesters, mPEG2-Aldehyde, mPEG2-ButyrALD, mPEG2-Forked Maleimide, mPEG2-N-Hydroxylsuccinimide, mPEG2-Maleimide, Multi-Arm PEGs and raw PEGs (all of which are available from Nektar Therapeutics, San Carlos, CA).

An IRM can be linked to a polymer with charged regions (+ or -) that enhance electrostatically favorable attachment of the IRM-polymer complex to antigens (e.g., expressed on cancer cell surfaces). Typically, under physiological conditions positively charged polymer-IRM complexes will bind to antigens with isoelectric points (pI) below 7, and negatively charged polymer-IRM complexes will bind to antigens with pIs above 7.

A mixture of IRMs linked to different molecular weights of polymer (and/or different polymers) may also achieve a desired release profile, and may be a way to influence the time course of immune response. For example, a pulsed release profile of an IRM, with 2-3 day spacing, can be therapeutically beneficial. Such a pulsed release of an IRM can avoid (or at least reduce the occurrence of) hyposensitization, local inflammation, and/or tolerance to treatment, while allowing dendritic cells enough time to be replenished by naïve ones at the site of a tumor, for example.

One or more IRMs can be attached to a polymer through either covalent attachment or non-covalent attachment. Non-covalent attachment of an IRM to a polymer carrier material includes attachment by ionic interaction or hydrogen bonding, for example.

Representative methods for covalently attaching an IRM to a polymer include chemical crosslinkers, such as heterobifunctional crosslinking compounds (i.e., "linkers")

that react to form a bond between reactive groups (such as hydroxyl, amino, amido, or  
sulfhydryl groups) in an immune response modifier and other reactive groups (of a similar  
nature) in the polymer. This bond may be, for example, a peptide bond, disulfide bond,  
thioester bond, amide bond, thioether bond, and the like. IRMs can also be covalently  
5 attached to a polymer by reacting an IRM containing a reactive group directly with a  
polymer containing a reactive group.

Immune response modifiers may be covalently bonded to a polymer by any of the  
methods known in the art. For example, U.S. Pat. Nos. 4,722,906, 4,979,959, 4,973,493,  
and 5,263,992 relate to devices having biocompatible agents covalently bound via a  
10 photoreactive group and a chemical linking moiety to the biomaterial surface. U.S. Pat.  
Nos. 5,258,041 and 5,217,492 relate to the attachment of biomolecules to a surface  
through the use of long chain chemical spacers. U.S. Pat. Nos. 5,002,582 and 5,263,992  
relate to the preparation and use of polymeric surfaces, wherein polymeric agents  
providing desirable properties are covalently bound via a photoreactive moiety to the  
15 surface.

In one embodiment, the IRM can be attached to a polymer using a linking group.  
The linking group can be any suitable organic linking group that allows the polymer to be  
covalently coupled to the immune response modifier moiety while preserving an effective  
amount of IRM activity. In some embodiments, the linker group can be a hydrolysable  
20 linker, enzymatic specific linker, or a protease specific linker. In some embodiments, the  
linking group may be selected to create sufficient space between the active core of the  
immune response modifier moiety and the polymer that the polymer does not interfere  
with a biologically effective interaction between the active core and the T cells that results  
in IRM activity such as cytokine production.

25 In this embodiment, the linking group includes a reactive group capable of reacting  
with a reactive group on the polymer to form a covalent bond. Suitable reactive groups  
include those discussed in Hermanson, G. (1996), *Bioconjugate Techniques*, Academic  
Press, Chapter 2 "The Chemistry of Reactive Functional Groups", 137-166. For example,  
the linking group may react with a primary amine (e.g., an N-hydroxysuccinimidyl ester or  
30 an N-hydroxysulfosuccinimidyl ester); it may react with a sulfhydryl group (e.g., a  
maleimide or an iodoacetyl), or it may be a photoreactive group (e.g. a phenyl azide

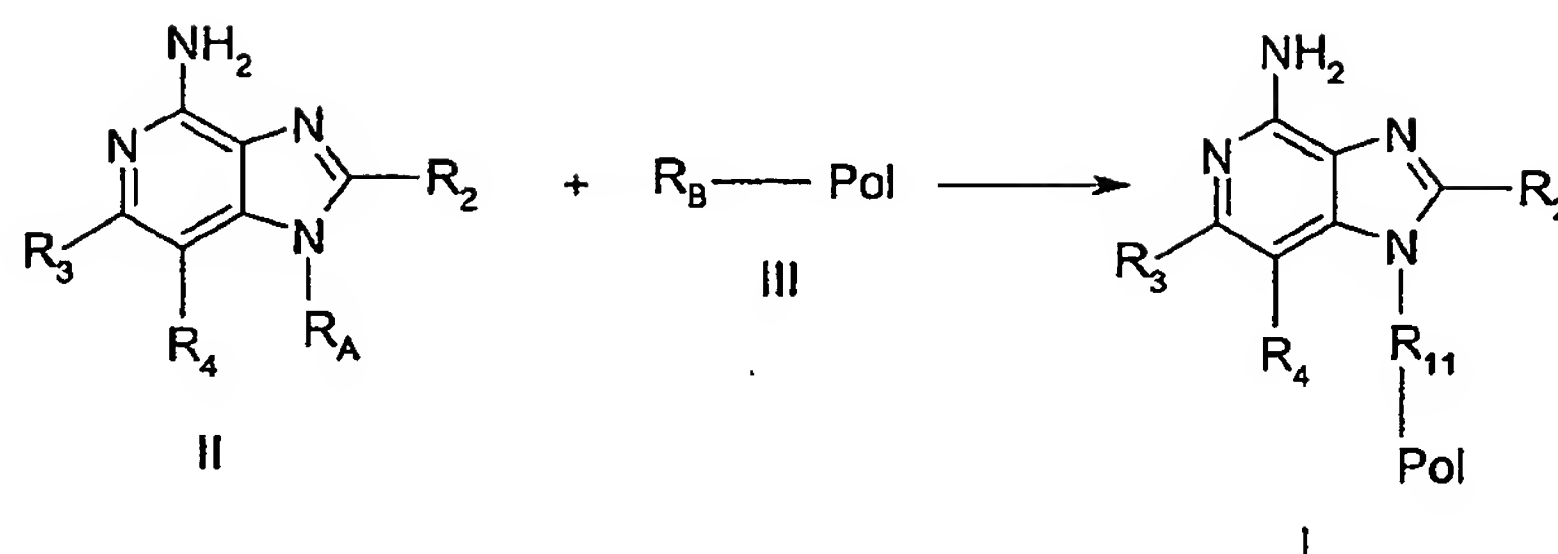
including 4-azidophenyl, 2-hydroxy-4-azidophenyl, 2-nitro-4-azidophenyl, and 2-nitro-3-azidophenyl).

5 In this embodiment, the polymer includes a chemically active group accessible for covalent coupling to the linking group. A chemically active group accessible for covalent coupling to the linking group includes groups that may be used directly for covalent coupling to the linking group or groups that may be modified to be available for covalent coupling to the linking group. For example, suitable chemically active groups include, but are not limited to, primary amines and sulfhydryl groups.

10 In certain embodiments, attachment may occur by reacting an immune response modifier with a crosslinker and then reacting the resulting intermediate with a polymer. Many crosslinkers suitable for such use are known and many are commercially available. See for example, Hermanson, G. (1996) *Bioconjugate Techniques*, Academic Press.

15 Attachment also may occur, for example, according to the method of Reaction Scheme I in which the polymer is linked to the IRM moiety through  $R_{11}$ . In Reaction Scheme I an IRM of Formula II is reacted with a polymer of Formula III to provide an IRM-polymer complex of Formula I.  $R_A$  and  $R_B$  each contain a functional group that is selected to react with the other. For example, if  $R_A$  contains a primary amine, then a polymer may be selected in which  $R_B$  contains an amine-reactive functional group such as an N-hydroxysuccinimidyl ester.  $R_A$  and  $R_B$  may be selected so that they react to provide  
20 the desired linker group in the IRM-polymer complex.

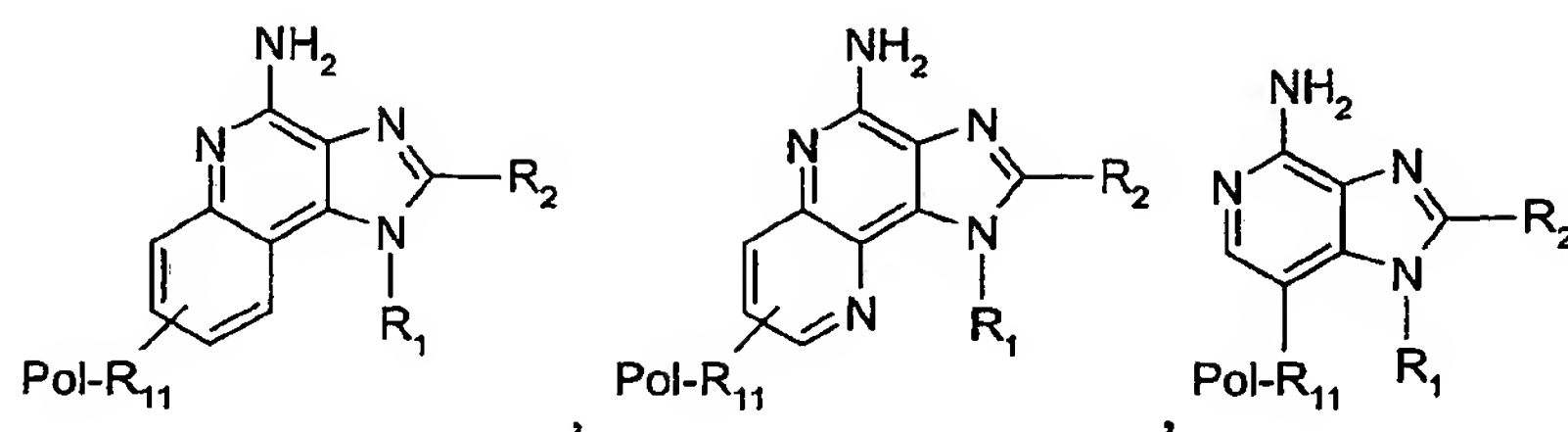
Methods for preparing compounds of Formula II where  $R_A$  contains a functional group are known. See, for example, U.S. Patent Nos. 4,689,338; 4,929,624; U.S. Patent No. 5,268,376; 5,389,640; 5,352,784; 5,494,916; 4,988,815; 5,367,076; 5,175,296; 5,395,937; 5,741,908; 5,693,811; 6,069,149; 6,194,425; 6,331,539; 6,451,810; 6,525,064; 25 6,541,485; 6,545,016; 6,545,017; 6,573,273; 6,656,938; 6,660,735; 6,660,747; 6,664,260; 6,664,264; 6,664,265; 6,667,312; 6,670,372; 6,677,347; 6,677,348; 6,677,349; 6,683,088; U.S. Patent Publications 2004/0147543 and 2004/0176367; and International Publication WO 03/103584. Many polymers containing  $R_B$  groups are known and many are commercially available. For example, activated polyethylene glycols available from  
30 Nektar, San Carlos, CA. Others can be prepared using known synthetic methods. See, for example, U.S. Patent No. 5,583,114 and the references cited therein.

Reaction Scheme I

5 The R groups (e.g., R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, and R<sub>4</sub>) can be hydrogen or organic groups that can optionally include various substitutions. They can include alkyl groups, alkenyl groups, including haloalkyl groups, aryl groups, heteroaryl groups, heterocyclyl groups, and the like.

For example, preferred R<sub>1</sub> groups include, alkyl groups having 1 to 4 carbon atoms, hydroxyalkyl groups having 1 to 4 carbon atoms (e.g., 2-hydroxy-2-methylpropyl),  
 10 methanesulfonylaminoalkyl groups wherein the alkyl group has 2 to 6 carbons (e.g. methanesulfonylaminoethyl, 2-methanesulfonylamino-2-methylpropyl); preferred R<sub>2</sub> groups include hydrogen, alkyl groups having 1 to 4 carbon atoms (i.e., methyl, ethyl, propyl, isopropyl, n-butyl, sec-butyl, isobutyl, tert-butyl, and cyclopropylmethyl), and alkoxyalkyl groups (e.g., methoxyethyl and ethoxymethyl). Preferably R<sub>3</sub> and R<sub>4</sub> are  
 15 independently hydrogen or methyl or R<sub>3</sub> and R<sub>4</sub> join together to form a benzene ring, a pyridine ring, a 6-membered saturated ring or a 6-membered saturated ring containing a nitrogen atom. One or more of these preferred substituents, if present, can be present in the compounds of the invention in any combination.

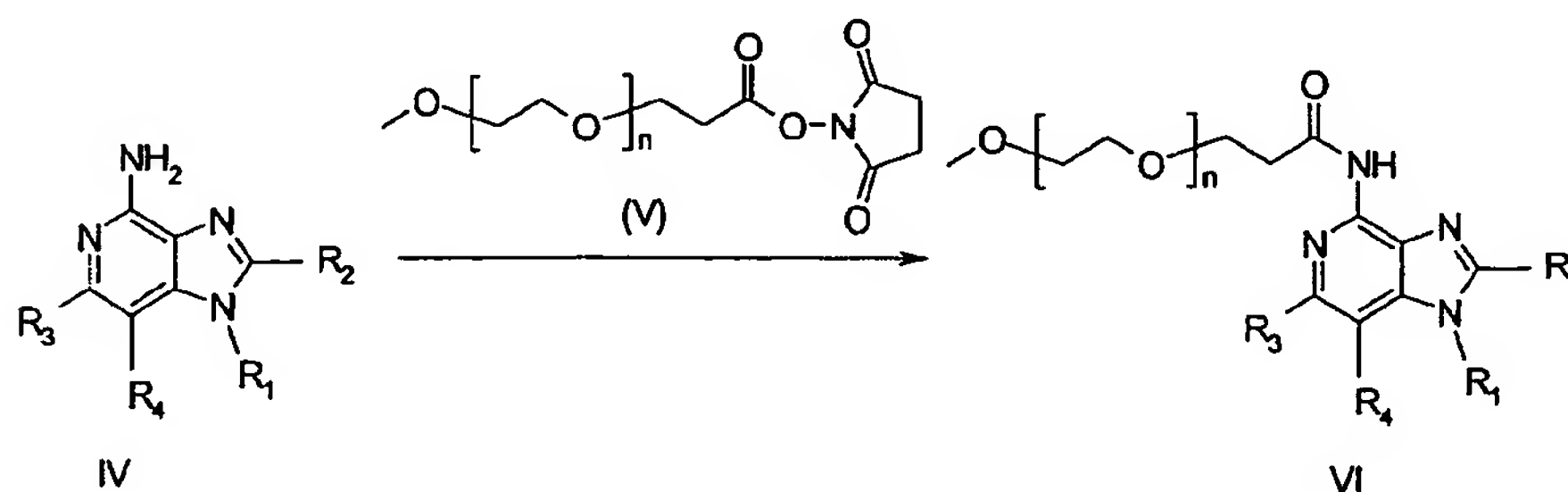
20 In Reaction Scheme I the IRM is attached to the polymer through a linking group at the N1 nitrogen of the imidazole ring. Alternatively the linking can occur at different positions on the ring system. Examples of which are shown below for imidazoquinoline amines, imidazonaphthyridine amines and imidazopyridine amines respectively.



The attachment is effected using the method of Reaction Scheme I starting with an IRM containing reactive group  $R_A$  at the desired attachment point. In another embodiment, the polymer group can be attached to the 4-amino group of an IRM. Attachment may occur, for example, using a variation of the method of Reaction Scheme I by reacting an IRM with  $R_B$ -polymer where  $R_B$  contains an amine-reactive functional group. Attachment may also occur using the methods described in Reaction Schemes II, III, IV, and V below.

In Reaction Scheme II, a polyethylene glycol polymer is attached to an IRM by the formation of an amide with the 4-amino group of the IRM. The reaction can be carried out by adding a succinimidyl propionate of Formula V to a solution of an IRM of Formula IV in a suitable solvent such as tetrahydrofuran. The reaction can be carried out at ambient temperature or at an elevated temperature such as 50°C. Some succinimidyl propionates of Formula V are commercially available; others can be prepared using conventional synthetic methods. Many IRMs of Formula IV are known (see Exemplary IRM Compounds below); preferably compounds wherein the  $R_1$ ,  $R_2$ ,  $R_3$ , and  $R_4$  groups do not contain a primary amine are selected.

#### Reaction Scheme II



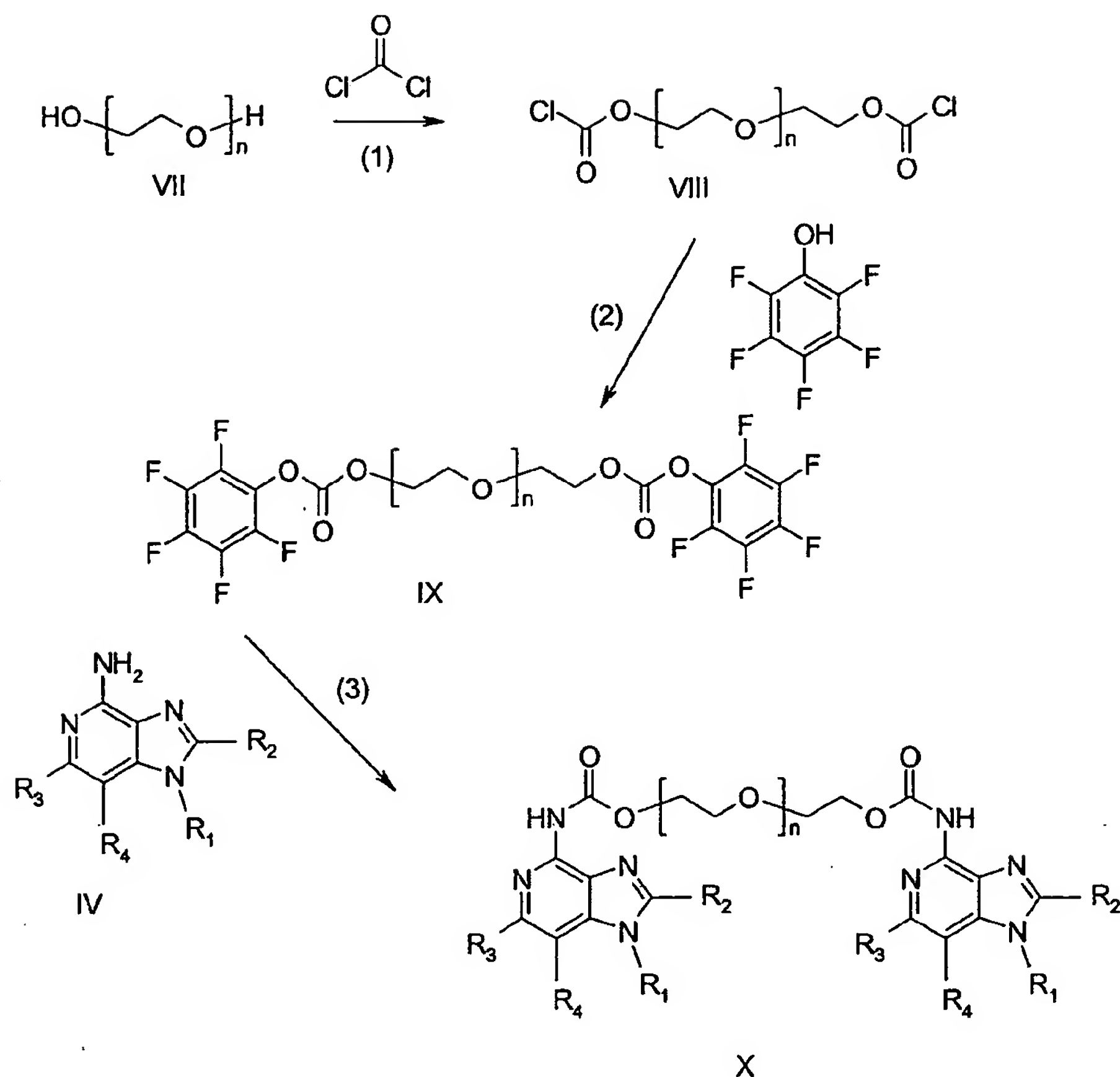
In Reaction Scheme III, a polyethylene glycol polymer is end capped with an IRM of Formula IV.

5 In step (1) of Reaction Scheme III, a polyethylene glycol polymer of Formula VII is reacted with phosgene to provide a bischloroformate of Formula VIII. The reaction can be carried out by treating a solution of a polymer of Formula VII in a suitable solvent such as toluene with an excess of phosgene. The reaction can be run at an elevated temperature such as about 45°C.

10 In step (2) of Reaction Scheme III, a bischloroformate of Formula VIII is reacted with pentafluorophenol to provide an activated carbonate of Formula IX. The reaction can be carried out by adding pentafluorophenol to a solution of a compound of Formula VIII in a suitable solvent such as toluene in the presence of a base such as triethylamine.

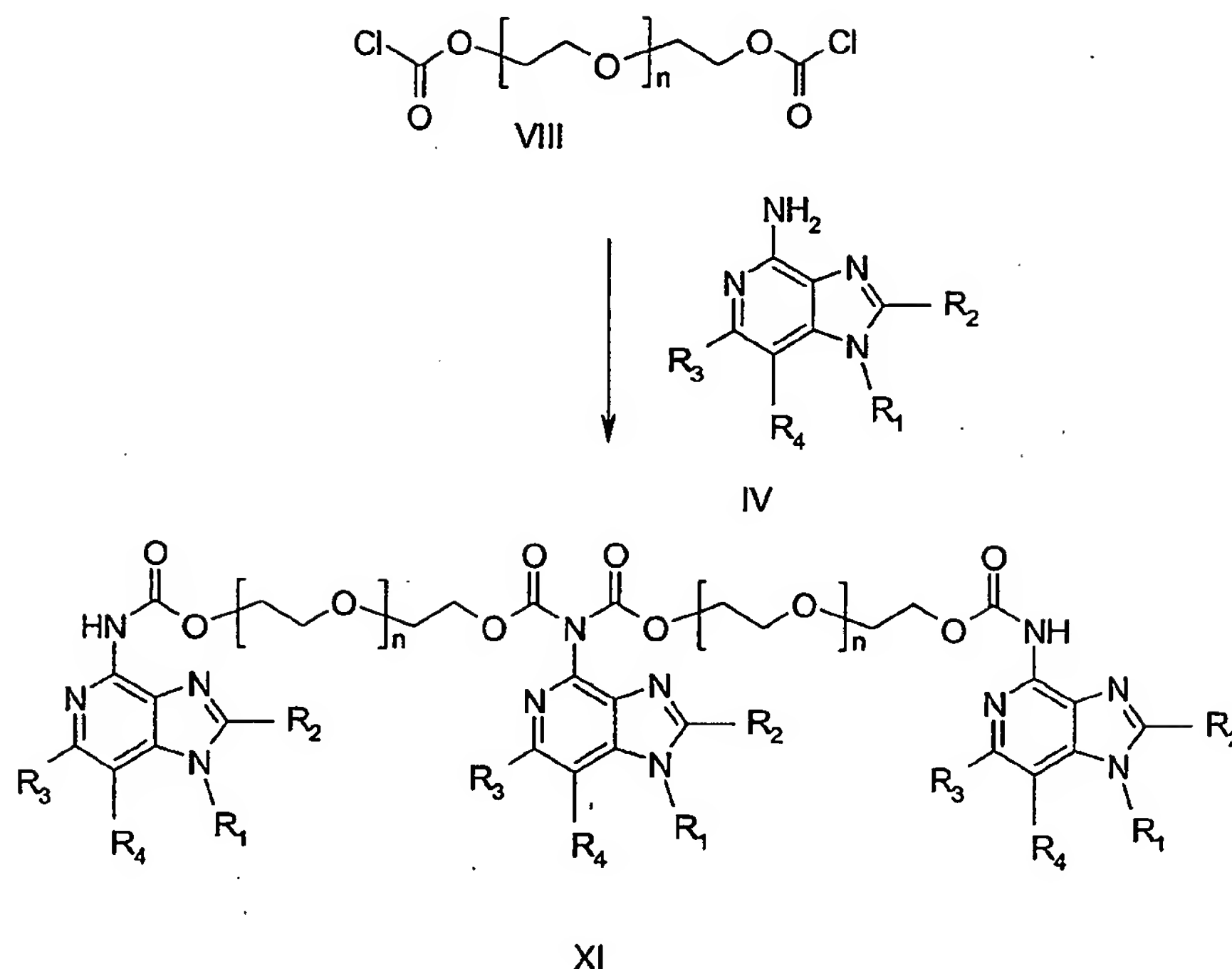
15 In step (3) of Reaction Scheme III, an activated carbonate of Formula IX is reacted with an IRM of Formula IV to provide an IRM substituted polyethylene glycol polymer of Formula X. The reaction can be carried out by treating a solution of a compound of Formula IX in a suitable solvent such as isopropanol with an IRM of Formula IV.

#### Reaction Scheme III



In Reaction Scheme IV, a polyethylene glycol polymer is chain extended with an IRM of Formula IV. The reaction can be carried out by adding  $m$  equivalents of a bischloroformate of Formula VIII to a solution containing  $m + 1$  equivalents of an IRM of Formula IV in a suitable solvent such as tetrahydrofuran in the presence of a base such as triethylamine. The reaction scheme illustrates 2 moles of a bischloroformate of Formula VIII reacting with 3 moles of an IRM of Formula IV

## Reaction Scheme IV



5           Reaction Scheme V illustrates the preparation of an IRM substituted multivalent polyethylene glycol polymer.

10           In step (1) of Reaction Scheme V, (2,5-diethyl-2-methyl-1,3-dioxan-5-yl)methanol is treated with phosgene to provide (2,5-diethyl-2-methyl-1,3-dioxan-5-yl)methyl chloridocarbonate. The reaction can be carried out by treating a solution of (2,5-diethyl-2-methyl-1,3-dioxan-5-yl)methanol in a suitable solvent such as toluene with phosgene.

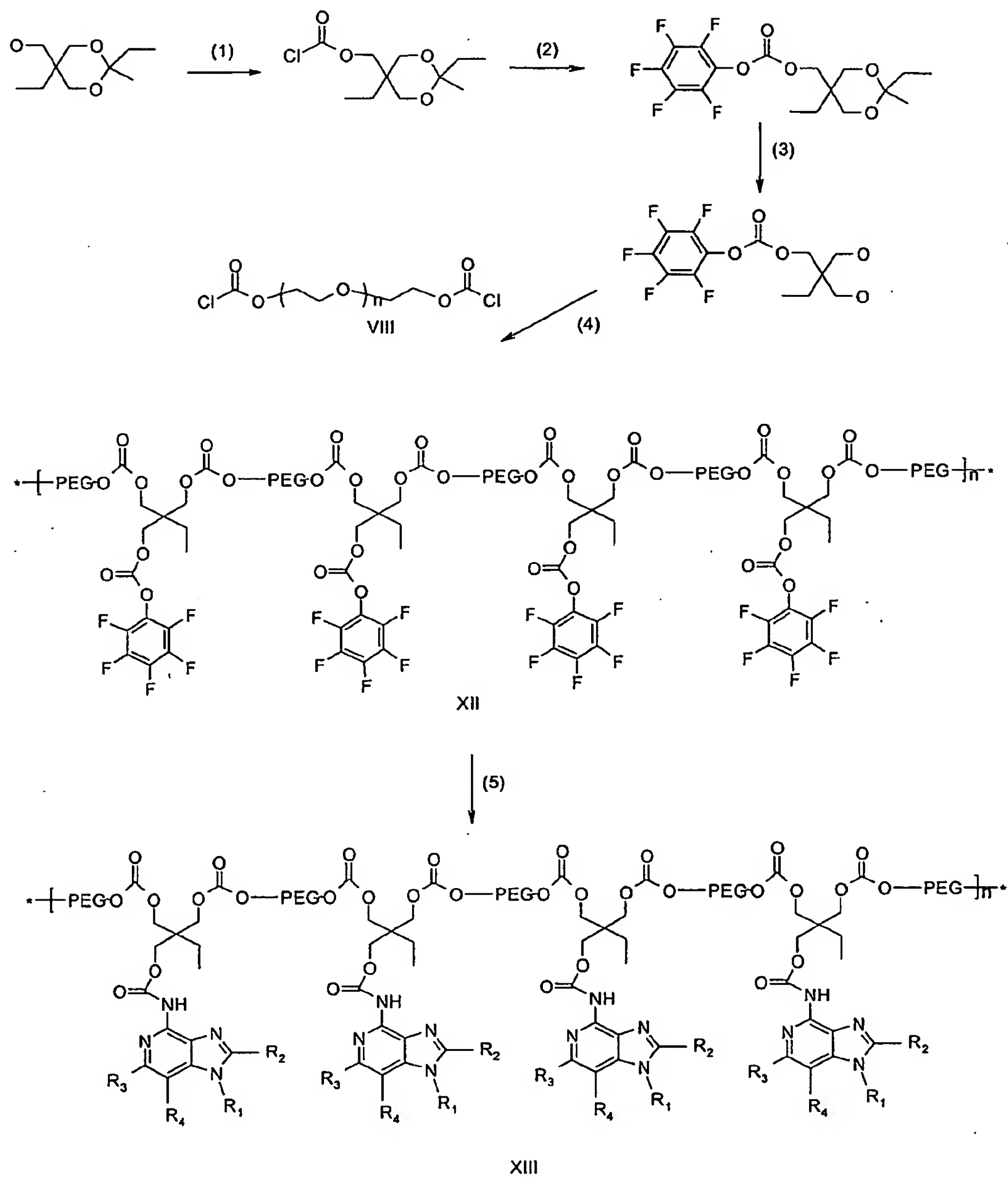
15           In step (2) of Reaction Scheme V, (2,5-diethyl-2-methyl-1,3-dioxan-5-yl)methyl chloridocarbonate is reacted with pentafluorophenol to provide (2,5-diethyl-2-methyl-1,3-dioxan-5-yl)methyl pentafluorophenyl carbonate. The reaction can be carried out by adding pentafluorophenol to a solution of (2,5-diethyl-2-methyl-1,3-dioxan-5-yl)methyl chloridocarbonate in a suitable solvent such as tetrahydrofuran in the presence of a base such as pyridine.

          In step (3) of Reaction Scheme V, (2,5-diethyl-2-methyl-1,3-dioxan-5-yl)methyl pentafluorophenyl carbonate is hydrolyzed under acidic conditions using conventional methods to provide 2,5-bis(hydroxymethyl)butyl pentafluorophenyl carbonate.

In step (4) of Reaction Scheme V, a bischloroformate of Formula VIII is reacted with 2,5-bis(hydroxymethyl)butyl pentafluorophenyl carbonate to provide a polyethylene glycol polymer of Formula XII containing activated carbonate groups. The reaction can be carried out as described in step (2) of Reaction Scheme III.

- 5 In step (5) of Reaction Scheme V, a polyethylene glycol polymer of Formula XII is reacted with an IRM of Formula IV to provide an IRM substituted multivalent polyethylene glycol polymer of Formula XIII. The reaction can be carried out as described in step (3) of Reaction Scheme III.

## Reaction Scheme V



5

*Delivery of IRM-Polymer Complexes*

The IRM preparations may be delivered via parenteral administration (by definition parenteral administration refers to non-oral administration, which would include

nasal, topical, ophthalmic, buccal, etc., but in practice usually refers to injectable products (intravenous, intramuscular, subcutaneous, intratumoral, etc.) using, e.g., needle injection, injection using a microneedle array, or any other known method for introducing a preparation parenterally. Once it is administered, the soluble IRM-polymer complex will typically automatically target a localized tissue region and/or tissue type (i.e., cell type). Delivery of the soluble IRM-polymer complex may be in conjunction with image guiding techniques using, for example, ultrasound, MRI, real-time X-ray (fluoroscopy), etc.

A "localized tissue region" will generally be a relatively small portion of the body, e.g., less than 10% by volume, and often less than 1% by volume. For example, depending on the size of, e.g., a solid tumor or cancerous organ, the localized tissue region will typically be on the order of no more than about 500 cm<sup>3</sup>, often less than about 100 cm<sup>3</sup>, and in many instances 10 cm<sup>3</sup> or less. For some applications the localized tissue region will be 1 cm<sup>3</sup> or less (e.g., for small tumor nodules, viral lesions, or vaccination sites). However, in certain instances the localized tissue region may be a particularly large region, up to several liters, for example, to treat metastasized cancer within the entire peritoneal cavity.

The IRM localized tissue region may be, e.g., a cancer, a viral infected lesion, or organ, or vaccination site. It may be a solid tumor, lymph tissue, reticuloendothelial system, bone marrow, mucosal tissue, etc. The localized tissue region may be, e.g., a breast cancer tumor, stomach cancer tumor, lung cancer tumor, head or neck cancer tumor, colorectal cancer tumor, renal cell carcinoma tumor, pancreatic cancer tumor, basal cell carcinoma tumor, pancreatic cancer tumor, cervical cancer tumor, melanoma cancer tumor, prostate cancer tumor, ovarian cancer tumor, or bladder cancer tumor.

#### 25 *Additional Agents*

In addition to one or more soluble IRM-polymer complexes, the IRM preparations (i.e., compositions) and methods of the present invention can include additional agents (particularly active agents), e.g., in admixture or administered separately. The additional agents can also be attached to the IRM-polymer complex (e.g., an antibody can be attached to the polymer or an IRM-antigen conjugate can be attached to the polymer).

Such additional agents may be additional active agents, including, for example, a chemotherapeutic agent, a cytotoxoid agent, an antibody, a cytokine, a vaccine or a tumor

necrosis factor receptor (TNFR) agonist. One or more IRMs that are not attached to the polymer carrier material can also be included.

Vaccines include any material that raises either humoral and/or cell mediated immune response, such as live or attenuated viral and bacterial immunogens and inactivated viral, tumor-derived, protozoal, organism-derived, fungal, and bacterial immunogens, toxoids, toxins, polysaccharides, proteins, glycoproteins, peptides, cellular vaccines, such as using dendritic cells, DNA vaccines, recombinant proteins, glycoproteins, and peptides, and the like, for use in connection with, e.g., cancer vaccines, BCG, cholera, plague, typhoid, hepatitis A, B, and C, influenza A and B, parainfluenza, polio, rabies, measles, mumps, rubella, yellow fever, tetanus, diphtheria, hemophilus influenza b, tuberculosis, meningococcal and pneumococcal vaccines, adenovirus, HIV, chicken pox, cytomegalovirus, dengue, feline leukemia, fowl plague, HSV-1 and HSV-2, hog cholera, Japanese encephalitis, respiratory syncytial virus, rotavirus, papilloma virus, severe acute respiratory syndrome (SARS), anthrax, and yellow fever. See also, e.g., vaccines disclosed in International Publication No. WO 02/24225. Such additional agents can include, but are not limited to, drugs, such as antiviral agents or cytokines. The vaccine may be separate or may be physically or chemically linked to the IRM, such as by chemical conjugation or other means, so that they are delivered as a unit. TNFR agonists that may be delivered in conjunction with the IRM preparation include, but are not limited to, CD40 receptor agonists, such as disclosed in copending application U.S. Patent Publication 2004/0141950. Other active ingredients for use in combination with an IRM preparation of the present invention include those disclosed in, e.g., U.S. Patent Publication No. 2003/0139364.

#### *Immune Response Modifier Compounds*

Immune response modifiers ("IRM") useful in the present invention include compounds that act on the immune system by inducing and/or suppressing cytokine biosynthesis. IRM compounds possess potent immunostimulating activity including, but not limited to, antiviral and antitumor activity, and can also down-regulate other aspects of the immune response, for example shifting the immune response away from a TH-2 immune response, which is useful for treating a wide range of TH-2 mediated diseases. IRM compounds can also be used to modulate humoral immunity by stimulating antibody

production by B cells. Further, various IRM compounds have been shown to be useful as vaccine adjuvants (see, e.g., U.S. Pat. Nos. 6,083,505 and 6,406,705, and International Publication No. WO 02/24225).

5 In particular, certain IRM compounds effect their immunostimulatory activity by inducing the production and secretion of cytokines such as, e.g., Type I interferons, TNF- $\alpha$ , IL-1, IL-6, IL-8, IL-10, IL-12, MIP-1, MIP-3 $\alpha$  and/or MCP-1, and can also inhibit production and secretion of certain TH-2 cytokines, such as IL-4 and IL-5. Some IRM compounds are said to suppress IL-1 and TNF (U.S. Pat. No. 6,518,265).

10 For some embodiments, the preferred IRM compounds are so-called small molecule IRMs, which are relatively small organic compounds (e.g., molecular weight under about 1000 daltons, preferably under about 500 daltons, as opposed to large biologic protein, peptides, and the like). Although not bound by any single theory of activity, some IRMs are known to be agonists of at least one Toll-like receptor (TLR). IRM compounds that are agonists for TLRs selected from 7 and/or 8 may be particularly useful for certain applications. In some applications, for example, the preferred IRM compound is not a TLR 7 agonist and is a TLR 8 agonist. In other applications, for example, the IRM is a TLR7 agonist and is not a TLR8 agonist. Some small molecule IRM compounds are agonists of TLRs such as 7 and/or 8 and perhaps others. Thus, in some embodiments, the IRM that is included in the soluble IRM-polymer complex may be a compound identified as an agonist of one or more TLRs.

20 For example, without being bound to any particular theory or mechanism of action, IRM compounds that activate a strong cytotoxic lymphocyte (CTL) response may be particularly desirable as vaccine adjuvants, especially for therapeutic viral and/or cancer vaccines because a therapeutic effect in these settings is dependent on the activation of cellular immunity. For example, studies have shown that activation of T cell immunity in a given patient has a significant positive effect on the prognosis of the patient. Therefore the ability to enhance T cell immunity is believed to be critical to producing a therapeutic effect in these disease settings.

25 IRM compounds that are TLR8 agonists may be particularly desirable for use with therapeutic cancer vaccines because antigen presenting cells that express TLR8 have been shown to produce IL-12 upon stimulation through TLR8. IL-12 is believed to play a

30

significant role in activation of CTLs, which are important for mediating therapeutic efficacy as described above.

IRM compounds that are TLR7 agonists may be particularly desirable for use with prophylactic vaccines because the type I interferon induced by stimulation through these  
5 TLRs is believed to contribute to the formation of neutralizing Th1-like humoral and cellular responses.

IRM compounds that are both TLR7 and TLR8 agonists may be particularly desirable for use with therapeutic viral vaccines and/or cancer vaccines because TLR7 stimulation is believed to induce the production of type I IFN and activation of innate cells  
10 such as macrophages and NK cells, and TLR8 stimulation is believed to activate antigen presenting cells to initiate cellular adaptive immunity as described above. These cell types are able to mediate viral clearance and/or therapeutic growth inhibitory effects against neoplasms.

IRM compounds that are non-TLR7 agonists, and do not induce substantial  
15 amounts of interferon alpha, may be desirable for use with certain vaccines such as bacterial vaccines because TLR7 induces type I IFN production, which down-regulates the production of IL-12 from macrophages and DCs. IL-12 contributes to the subsequent activation of macrophages, NK cells and CTLs, all of which contribute to anti-bacterial immunity. Therefore the induction of anti-bacterial immunity against some kinds of  
20 bacteria may be enhanced in the absence of IFN $\alpha$ .

For purposes of the present application, one way to determine if an IRM compound is considered to be an agonist for a particular TLR is if it activates an NF $\kappa$ B/luciferase reporter construct through that TLR from the target species more than about 1.5 fold, and usually at least about 2 fold, in TLR transfected host cells such as, e.g., HEK293 or  
25 Namalwa cells relative to control transfectants. For information regarding TLR activation, see, e.g., International Patent Publication Nos. WO 03/043573 and WO 03/043588, U.S. Patent Publication Nos. US2004/0014779, US2004/0132079; 2004/0162309; US2004/0171086, and US2004/0197865; and the other IRM patents and applications disclosed herein.

30 Preferred IRM compounds include a 2-aminopyridine fused to a five-membered nitrogen-containing heterocyclic ring.

Examples of classes of small molecule IRM compounds include, but are not limited to, imidazoquinoline amines including but not limited to substituted imidazoquinoline amines such as, for example, amide substituted imidazoquinoline amines, sulfonamide substituted imidazoquinoline amines, urea substituted imidazoquinoline amines, aryl ether substituted imidazoquinoline amines, heterocyclic ether substituted imidazoquinoline amines, amido ether substituted imidazoquinoline amines, sulfonamido ether substituted imidazoquinoline amines, urea substituted imidazoquinoline ethers, thioether substituted imidazoquinoline amines, 6-, 7-, 8-, or 9-aryl, heteroaryl, aryloxy or arylalkyleneoxy substituted imidazoquinoline amines, and imidazoquinoline diamines; tetrahydroimidazoquinoline amines including but not limited to amide substituted tetrahydroimidazoquinoline amines, sulfonamide substituted tetrahydroimidazoquinoline amines, urea substituted tetrahydroimidazoquinoline amines, aryl ether substituted tetrahydroimidazoquinoline amines, heterocyclic ether substituted tetrahydroimidazoquinoline amines, amido ether substituted tetrahydroimidazoquinoline amines, sulfonamido ether substituted tetrahydroimidazoquinoline amines, urea substituted tetrahydroimidazoquinoline ethers, thioether substituted tetrahydroimidazoquinoline amines, and tetrahydroimidazoquinoline diamines; imidazopyridine amines including but not limited to amide substituted imidazopyridine amines, sulfonamide substituted imidazopyridine amines, urea substituted imidazopyridine amines, aryl ether substituted imidazopyridine amines, heterocyclic ether substituted imidazopyridine amines, amido ether substituted imidazopyridine amines, sulfonamido ether substituted imidazopyridine amines, urea substituted imidazopyridine ethers, and thioether substituted imidazopyridine amines; 1,2-bridged imidazoquinoline amines; 6,7-fused cycloalkylimidazopyridine amines; imidazonaphthyridine amines; tetrahydroimidazonaphthyridine amines; oxazoloquinoline amines; thiazoloquinoline amines; oxazolopyridine amines; thiazolopyridine amines; oxazolonaphthyridine amines; thiazolonaphthyridine amines; and 1*H*-imidazo dimers fused to pyridine amines, quinoline amines, tetrahydroquinoline amines, naphthyridine amines, or tetrahydronaphthyridine amines, such as those disclosed in, for example, U.S. Pat. 4,689,338; 4,929,624; 5,266,575; 5,268,376; 5,346,905; 5,352,784; 5,389,640; 5,446,153; 5,482,936; 5,756,747; 6,110,929; 6,194,425; 6,331,539; 6,376,669; 6,451,810; 6,525,064; 6,541,485; 6,545,016; 6,545,017; 6,573,273; 6,656,938; 6,660,735; 6,660,747; 6,664,260; 6,664,264; 6,664,265; 6,667,312; 6,670,372; 6,677,347;

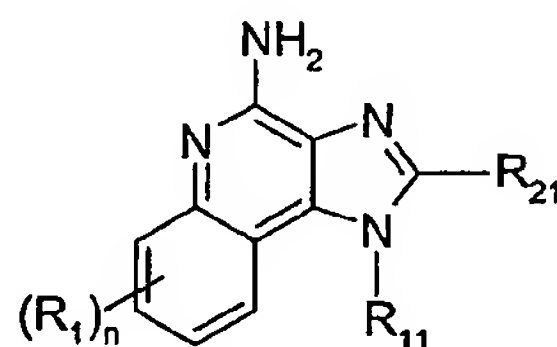
6,677,348; 6,677,349; 6,683,088; 6,756,382; 6,797,718; and 6,818,650; and U.S. Patent Publication Nos. 2004/0091491; 2004/0147543; and 2004/0176367.

Additional examples of small molecule IRMs said to induce interferon (among other things) include purine derivatives (such as those described in U.S. Pat. Nos. 6,376,501, and 6,028,076), imidazoquinoline amide derivatives (such as those described in U.S. Pat. No. 6,069,149), and benzimidazole derivatives (such as those described in U.S. Pat. No. 6,387,938). 1H-imidazopyridine derivatives (such as those described in U.S. Pat. No. 6,518,265) are said to inhibit TNF and IL-1 cytokines. Other small molecule IRMs said to be TLR 7 agonists are shown in U.S. 2003/0199461 A1.

Examples of small molecule IRMs that include a 4-aminopyrimidine fused to a five-membered nitrogen-containing heterocyclic ring include adenine derivatives (such as those described in U. S. Pat. Nos. 6,376,501; 6,028,076 and 6,329,381; and in WO 02/08595).

#### Exemplary IRM Compounds

As noted above, many of the IRM compounds useful in the present invention have demonstrated immunomodulating activity. In certain embodiments of the present invention the IRM compound can be chosen from 1H-imidazo[4,5-c]quinolin-4-amines defined by one of Formulas I-V below:



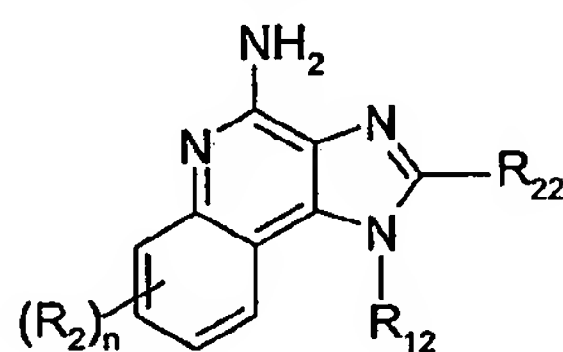
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wherein

R<sub>11</sub> is selected from alkyl of one to ten carbon atoms, hydroxyalkyl of one to six carbon atoms, acyloxyalkyl wherein the acyloxy moiety is alkanoyloxy of two to four carbon atoms or benzoyloxy, and the alkyl moiety contains one to six carbon atoms, benzyl, (phenyl)ethyl and phenyl, said benzyl, (phenyl)ethyl or phenyl substituent being optionally substituted on the benzene ring by one or two moieties independently selected from alkyl of one to four carbon atoms, alkoxy of one to four carbon atoms and halogen, with the proviso that if said benzene ring is substituted by two of said moieties, then said moieties together contain no more than six carbon atoms;

5  $R_{21}$  is selected from hydrogen, alkyl of one to eight carbon atoms, benzyl, (phenyl)ethyl and phenyl, the benzyl, (phenyl)ethyl or phenyl substituent being optionally substituted on the benzene ring by one or two moieties independently selected from alkyl of one to four carbon atoms, alkoxy of one to four carbon atoms and halogen, with the proviso that when the benzene ring is substituted by two of said moieties, then the moieties together contain no more than six carbon atoms; and

each  $R_1$  is independently selected from alkoxy of one to four carbon atoms, halogen, and alkyl of one to four carbon atoms, and  $n$  is an integer from 0 to 2, with the proviso that if  $n$  is 2, then said  $R_1$  groups together contain no more than six carbon atoms;



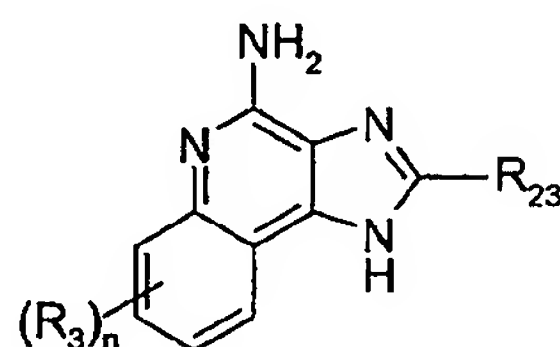
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wherein

15  $R_{12}$  is selected from straight chain or branched chain alkenyl containing two to ten carbon atoms and substituted straight chain or branched chain alkenyl containing two to ten carbon atoms, wherein the substituent is selected from straight chain or branched chain alkyl containing one to four carbon atoms and cycloalkyl containing three to six carbon atoms; and cycloalkyl containing three to six carbon atoms substituted by straight chain or branched chain alkyl containing one to four carbon atoms; and

20  $R_{22}$  is selected from hydrogen, straight chain or branched chain alkyl containing one to eight carbon atoms, benzyl, (phenyl)ethyl and phenyl, the benzyl, (phenyl)ethyl or phenyl substituent being optionally substituted on the benzene ring by one or two moieties independently selected from straight chain or branched chain alkyl containing one to four carbon atoms, straight chain or branched chain alkoxy containing one to four carbon atoms, and halogen, with the proviso that when the benzene ring is substituted by two such moieties, then the moieties together contain no more than six carbon atoms; and

25 each  $R_2$  is independently selected from straight chain or branched chain alkoxy containing one to four carbon atoms, halogen, and straight chain or branched chain alkyl containing one to four carbon atoms, and  $n$  is an integer from zero to 2, with the proviso that if  $n$  is 2, then said  $R_2$  groups together contain no more than six carbon atoms;

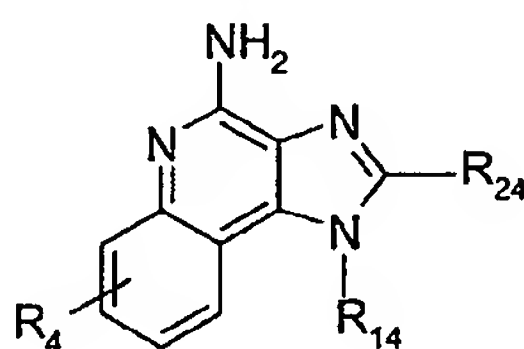


III

wherein

$R_{23}$  is selected from hydrogen, straight chain or branched chain alkyl of one to eight carbon atoms, benzyl, (phenyl)ethyl and phenyl, the benzyl, (phenyl)ethyl or phenyl substituent being optionally substituted on the benzene ring by one or two moieties independently selected from straight chain or branched chain alkyl of one to four carbon atoms, straight chain or branched chain alkoxy of one to four carbon atoms, and halogen, with the proviso that when the benzene ring is substituted by two such moieties, then the moieties together contain no more than six carbon atoms; and

each  $R_3$  is independently selected from straight chain or branched chain alkoxy of one to four carbon atoms, halogen, and straight chain or branched chain alkyl of one to four carbon atoms, and  $n$  is an integer from zero to 2, with the proviso that if  $n$  is 2, then said  $R_3$  groups together contain no more than six carbon atoms;



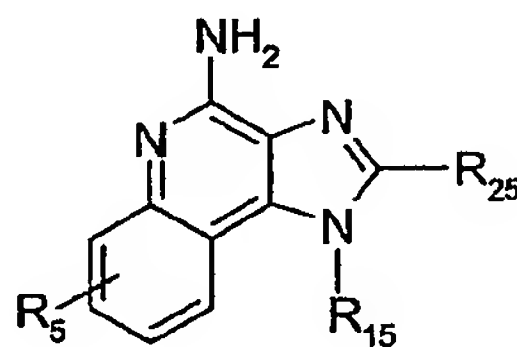
IV

wherein

$R_{14}$  is  $-\text{CHR}_x\text{R}_y$  wherein  $\text{R}_y$  is hydrogen or a carbon-carbon bond, with the proviso that when  $\text{R}_y$  is hydrogen  $\text{R}_x$  is alkoxy of one to four carbon atoms, hydroxyalkoxy of one to four carbon atoms, 1-alkynyl of two to ten carbon atoms, tetrahydropyranyl, alkoxyalkyl wherein the alkoxy moiety contains one to four carbon atoms and the alkyl moiety contains one to four carbon atoms, or 2-, 3-, or 4-pyridyl, and with the further proviso that when  $\text{R}_y$  is a carbon-carbon bond  $\text{R}_y$  and  $\text{R}_x$  together form a tetrahydrofuranyl group optionally substituted with one or more substituents independently selected from hydroxy and hydroxyalkyl of one to four carbon atoms;

$R_{24}$  is selected from hydrogen, alkyl of one to four carbon atoms, phenyl, and substituted phenyl wherein the substituent is selected from alkyl of one to four carbon atoms, alkoxy of one to four carbon atoms, and halogen; and

$R_4$  is selected from hydrogen, straight chain or branched chain alkoxy containing one to four carbon atoms, halogen, and straight chain or branched chain alkyl containing one to four carbon atoms;

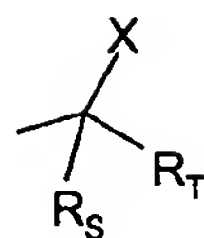


V

wherein

$R_{15}$  is selected from hydrogen; straight chain or branched chain alkyl containing one to ten carbon atoms and substituted straight chain or branched chain alkyl containing one to ten carbon atoms, wherein the substituent is selected from cycloalkyl containing three to six carbon atoms and cycloalkyl containing three to six carbon atoms substituted by straight chain or branched chain alkyl containing one to four carbon atoms; straight chain or branched chain alkenyl containing two to ten carbon atoms and substituted straight chain or branched chain alkenyl containing two to ten carbon atoms, wherein the substituent is selected from cycloalkyl containing three to six carbon atoms and cycloalkyl containing three to six carbon atoms substituted by straight chain or branched chain alkyl containing one to four carbon atoms; hydroxyalkyl of one to six carbon atoms; alkoxyalkyl wherein the alkoxy moiety contains one to four carbon atoms and the alkyl moiety contains one to six carbon atoms; acyloxyalkyl wherein the acyloxy moiety is alkanoyloxy of two to four carbon atoms or benzoyloxy, and the alkyl moiety contains one to six carbon atoms; benzyl; (phenyl)ethyl; and phenyl; said benzyl, (phenyl)ethyl or phenyl substituent being optionally substituted on the benzene ring by one or two moieties independently selected from alkyl of one to four carbon atoms, alkoxy of one to four carbon atoms, and halogen, with the proviso that when said benzene ring is substituted by two of said moieties, then the moieties together contain no more than six carbon atoms;

R<sub>25</sub> is



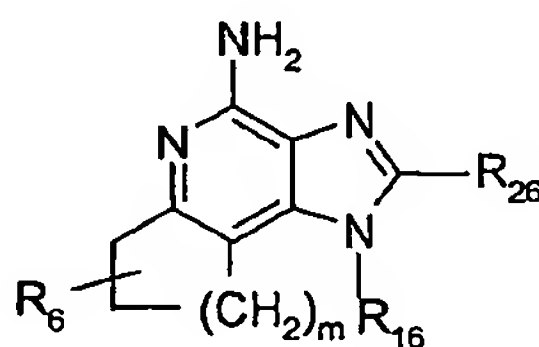
wherein

R<sub>5</sub> and R<sub>T</sub> are independently selected from hydrogen, alkyl of one to four carbon atoms, phenyl, and substituted phenyl wherein the substituent is selected from alkyl of one to four carbon atoms, alkoxy of one to four carbon atoms, and halogen;

X is selected from alkoxy containing one to four carbon atoms, alkoxyalkyl wherein the alkoxy moiety contains one to four carbon atoms and the alkyl moiety contains one to four carbon atoms, hydroxyalkyl of one to four carbon atoms, haloalkyl of one to four carbon atoms, alkylamido wherein the alkyl group contains one to four carbon atoms, amino, substituted amino wherein the substituent is alkyl or hydroxyalkyl of one to four carbon atoms, azido, chloro, hydroxy, 1-morpholino, 1-pyrrolidino, alkylthio of one to four carbon atoms; and

R<sub>5</sub> is selected from hydrogen, straight chain or branched chain alkoxy containing one to four carbon atoms, halogen, and straight chain or branched chain alkyl containing one to four carbon atoms; and pharmaceutically acceptable salts of any of the foregoing.

In another embodiment, the IRM compound can be chosen from 6,7 fused cycloalkylimidazopyridine amines defined by Formula VI below:



VI

wherein

m is 1, 2, or 3;

R<sub>16</sub> is selected from hydrogen; cyclic alkyl of three, four, or five carbon atoms; straight chain or branched chain alkyl containing one to ten carbon atoms and substituted straight chain or branched chain alkyl containing one to ten carbon atoms, wherein the substituent is selected from cycloalkyl containing three to six carbon atoms and cycloalkyl

containing three to six carbon atoms substituted by straight chain or branched chain alkyl containing one to four carbon atoms; fluoro- or chloroalkyl containing from one to ten carbon atoms and one or more fluorine or chlorine atoms; straight chain or branched chain alkenyl containing two to ten carbon atoms and substituted straight chain or branched chain alkenyl containing two to ten carbon atoms, wherein the substituent is selected from cycloalkyl containing three to six carbon atoms and cycloalkyl containing three to six carbon atoms substituted by straight chain or branched chain alkyl containing one to four carbon atoms; hydroxyalkyl of one to six carbon atoms; alkoxyalkyl wherein the alkoxy moiety contains one to four carbon atoms and the alkyl moiety contains one to six carbon atoms; acyloxyalkyl wherein the acyloxy moiety is alkanoyloxy of two to four carbon atoms or benzoyloxy, and the alkyl moiety contains one to six carbon atoms, with the proviso that any such alkyl, substituted alkyl, alkenyl, substituted alkenyl, hydroxyalkyl, alkoxyalkyl, or acyloxyalkyl group does not have a fully carbon substituted carbon atom bonded directly to the nitrogen atom; benzyl; (phenyl)ethyl; and phenyl; said benzyl, (phenyl)ethyl or phenyl substituent being optionally substituted on the benzene ring by one or two moieties independently selected from alkyl of one to four carbon atoms, alkoxy of one to four carbon atoms, and halogen, with the proviso that when said benzene ring is substituted by two of said moieties, then the moieties together contain no more than six carbon atoms; and  $-\text{CHR}_x\text{R}_y$  wherein

$\text{R}_y$  is hydrogen or a carbon-carbon bond, with the proviso that when  $\text{R}_y$  is hydrogen  $\text{R}_x$  is alkoxy of one to four carbon atoms, hydroxyalkoxy of one to four carbon atoms, 1-alkynyl of two to ten carbon atoms, tetrahydropyranyl, alkoxyalkyl wherein the alkoxy moiety contains one to four carbon atoms and the alkyl moiety contains one to four carbon atoms, 2-, 3-, or 4-pyridyl, and with the further proviso that when  $\text{R}_y$  is a carbon-carbon bond  $\text{R}_y$  and  $\text{R}_x$  together form a tetrahydrofuranyl group optionally substituted with one or more substituents independently selected from hydroxy and hydroxyalkyl of one to four carbon atoms,

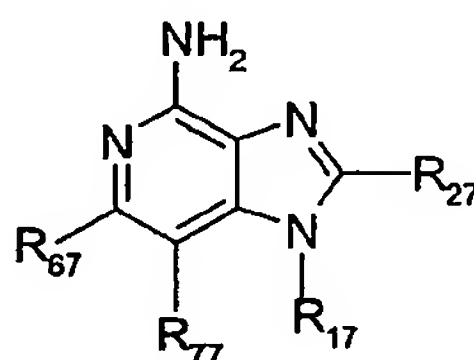
$\text{R}_{26}$  is selected from hydrogen; straight chain or branched chain alkyl containing one to eight carbon atoms; straight chain or branched chain hydroxyalkyl containing one to six carbon atoms; morpholinoalkyl; benzyl; (phenyl)ethyl; and phenyl, the benzyl, (phenyl)ethyl, or phenyl substituent being optionally substituted on the benzene ring by a

moiety selected from methyl, methoxy, and halogen; and  $-C(R_S)(R_T)(X)$  wherein  $R_S$  and  $R_T$  are independently selected from hydrogen, alkyl of one to four carbon atoms, phenyl, and substituted phenyl wherein the substituent is selected from alkyl of one to four carbon atoms, alkoxy of one to four carbon atoms, and halogen;

5 X is selected from alkoxy containing one to four carbon atoms, alkoxyalkyl wherein the alkoxy moiety contains one to four carbon atoms and the alkyl moiety contains one to four carbon atoms, haloalkyl of one to four carbon atoms, alkylamido wherein the alkyl group contains one to four carbon atoms, amino, substituted amino wherein the substituent is alkyl or hydroxyalkyl of one to four carbon atoms, azido,  
10 alkylthio of one to four carbon atoms, and morpholinoalkyl wherein the alkyl moiety contains one to four carbon atoms, and

$R_6$  is selected from hydrogen, fluoro, chloro, straight chain or branched chain alkyl containing one to four carbon atoms, and straight chain or branched chain fluoro- or chloroalkyl containing one to four carbon atoms and at least one fluorine or chlorine atom;  
15 and pharmaceutically acceptable salts thereof.

In another embodiment, the IRM compound can be chosen from imidazopyridine amines defined by Formula VII below:



VII

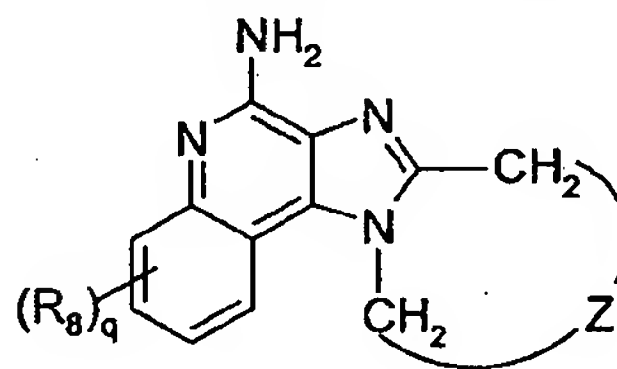
20 wherein

$R_{17}$  is selected from hydrogen;  $-CH_2R_W$  wherein  $R_W$  is selected from straight chain, branched chain, or cyclic alkyl containing one to ten carbon atoms, straight chain or branched chain alkenyl containing two to ten carbon atoms, straight chain or branched chain hydroxyalkyl containing one to six carbon atoms, alkoxyalkyl wherein the alkoxy  
25 moiety contains one to four carbon atoms and the alkyl moiety contains one to six carbon atoms, and phenylethyl; and  $-CH=CR_ZR_Z$  wherein each  $R_Z$  is independently straight chain, branched chain, or cyclic alkyl of one to six carbon atoms;

$R_{27}$  is selected from hydrogen; straight chain or branched chain alkyl containing one to eight carbon atoms; straight chain or branched chain hydroxyalkyl containing one to six carbon atoms; alkoxyalkyl wherein the alkoxy moiety contains one to four carbon atoms and the alkyl moiety contains one to six carbon atoms; benzyl, (phenyl)ethyl and phenyl, the benzyl, (phenyl)ethyl and phenyl being optionally substituted on the benzene ring by a moiety selected from methyl, methoxy, and halogen; and morpholinoalkyl wherein the alkyl moiety contains one to four carbon atoms;

$R_{67}$  and  $R_{77}$  are independently selected from hydrogen and alkyl of one to five carbon atoms, with the proviso that  $R_{67}$  and  $R_{77}$  taken together contain no more than six carbon atoms, and with the further proviso that when  $R_{77}$  is hydrogen then  $R_{67}$  is other than hydrogen and  $R_{27}$  is other than hydrogen or morpholinoalkyl, and with the further proviso that when  $R_{67}$  is hydrogen then  $R_{77}$  and  $R_{27}$  are other than hydrogen; and pharmaceutically acceptable salts thereof.

In another embodiment, the IRM compound can be chosen from 1,2-bridged imidazoquinoline amines defined by Formula VIII below:



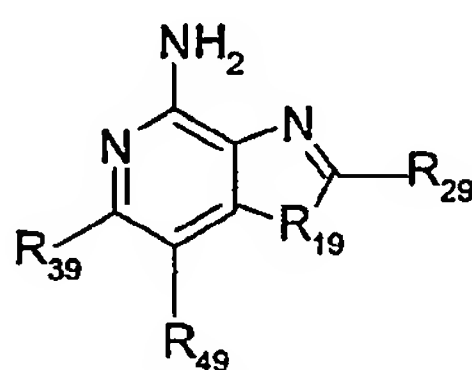
VIII

wherein

- $Z$  is selected from
- $-(CH_2)_p-$  wherein  $p$  is 1 to 4;
  - $-(CH_2)_a-C(R_D R_E)(CH_2)_b-$ , wherein  $a$  and  $b$  are integers and  $a+b$  is 0 to 3,  $R_D$  is hydrogen or alkyl of one to four carbon atoms, and  $R_E$  is selected from alkyl of one to four carbon atoms, hydroxy,  $-OR_F$  wherein  $R_F$  is alkyl of one to four carbon atoms, and  $-NR_G R'_G$  wherein  $R_G$  and  $R'_G$  are independently hydrogen or alkyl of one to four carbon atoms; and
  - $-(CH_2)_a-(Y)-(CH_2)_b-$  wherein  $a$  and  $b$  are integers and  $a+b$  is 0 to 3, and  $Y$  is O, S, or  $-NR_J-$  wherein  $R_J$  is hydrogen or alkyl of one to four carbon atoms;
- $q$  is 0 or 1; and

R<sub>8</sub> is selected from alkyl of one to four carbon atoms, alkoxy of one to four carbon atoms, and halogen,  
and pharmaceutically acceptable salts thereof.

In another embodiment, the IRM compound can be chosen from thiazoloquinoline  
amines, oxazoloquinoline amines, thiazolopyridine amines, oxazolopyridine amines,  
thiazolonaphthyridine amines and oxazolonaphthyridine amines defined by Formula IX  
below:



IX

wherein:

R<sub>19</sub> is selected from oxygen, sulfur and selenium;

R<sub>29</sub> is selected from

- hydrogen;
- alkyl;
- alkyl-OH;
- haloalkyl;
- alkenyl;
- alkyl-X-alkyl;
- alkyl-X-alkenyl;
- alkenyl-X-alkyl;
- alkenyl-X-alkenyl;
- alkyl-N(R<sub>59</sub>)<sub>2</sub>;
- alkyl-N<sub>3</sub>;
- alkyl-O-C(O)-N(R<sub>59</sub>)<sub>2</sub>;
- heterocyclyl;
- alkyl-X-heterocyclyl;
- alkenyl-X-heterocyclyl;
- aryl;

-alkyl-X-aryl;  
 -alkenyl-X-aryl;  
 -heteroaryl;  
 -alkyl-X-heteroaryl; and  
 -alkenyl-X-heteroaryl;

$R_{39}$  and  $R_{49}$  are each independently:

-hydrogen;  
 -X-alkyl;  
 -halo;  
 -haloalkyl;  
 - $N(R_{59})_2$ ;

or when taken together,  $R_{39}$  and  $R_{49}$  form a fused aromatic, heteroaromatic, cycloalkyl or heterocyclic ring;

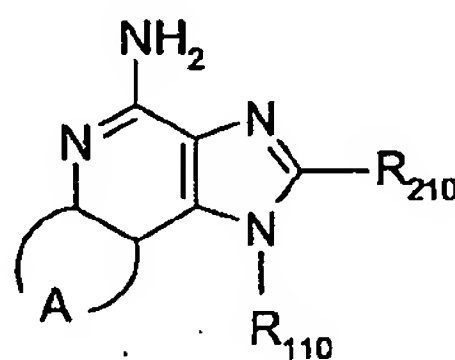
X is selected from -O-, -S-, - $NR_{59}$ -, -C(O)-, -C(O)O-, -OC(O)-, and a bond;

and

each  $R_{59}$  is independently H or  $C_{1-8}$ alkyl;

and pharmaceutically acceptable salts thereof.

In another embodiment, the IRM compound can be chosen from imidazonaphthyridine amines and imidazotetrahydronaphthyridine amines defined by Formulas X and XI below:



X

wherein

A is =N-CR=CR-CR=; =CR-N=CR-CR=; =CR-CR=N-CR=; or

=CR-CR=CR-N=;

$R_{110}$  is selected from:

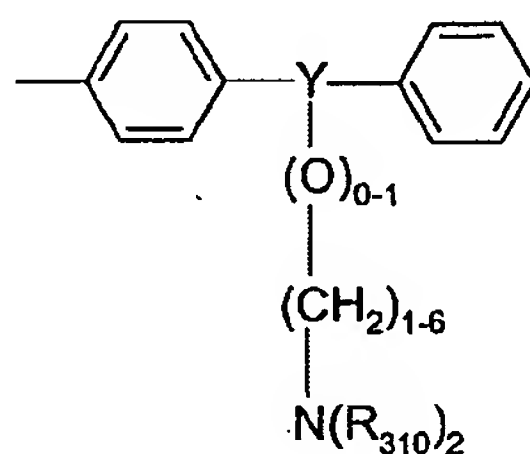
- hydrogen;

- $C_{1-20}$  alkyl or  $C_{2-20}$  alkenyl that is unsubstituted or substituted by one or more

substituents selected from:

- aryl;
- heteroaryl;
- heterocyclyl;
- O-C<sub>1-20</sub> alkyl;
- 5 -O-(C<sub>1-20</sub> alkyl)<sub>0-1</sub>-aryl;
- O-(C<sub>1-20</sub> alkyl)<sub>0-1</sub>-heteroaryl;
- O-(C<sub>1-20</sub> alkyl)<sub>0-1</sub>-heterocyclyl;
- CO-O-C<sub>1-20</sub> alkyl;
- S(O)<sub>0-2</sub>-C<sub>1-20</sub> alkyl;
- 10 -S(O)<sub>0-2</sub>-(C<sub>1-20</sub> alkyl)<sub>0-1</sub>-aryl;
- S(O)<sub>0-2</sub>-(C<sub>1-20</sub> alkyl)<sub>0-1</sub>-heteroaryl;
- S(O)<sub>0-2</sub>-(C<sub>1-20</sub> alkyl)<sub>0-1</sub>-heterocyclyl;
- N(R<sub>310</sub>)<sub>2</sub>;
- N<sub>3</sub>;
- 15 oxo;
- halogen;
- NO<sub>2</sub>;
- OH; and
- SH; and
- 20 -C<sub>1-20</sub> alkyl-NR<sub>310</sub>-Q-X-R<sub>410</sub> or -C<sub>2-20</sub> alkenyl-NR<sub>310</sub>-Q-X-R<sub>410</sub> wherein Q is -CO- or -SO<sub>2</sub>-; X is a bond, -O- or -NR<sub>310</sub>- and R<sub>410</sub> is aryl; heteroaryl; heterocyclyl; or -C<sub>1-20</sub> alkyl or C<sub>2-20</sub> alkenyl that is unsubstituted or substituted by one or more substituents selected from:
- aryl;
- 25 -heteroaryl;
- heterocyclyl;
- O-C<sub>1-20</sub> alkyl;
- O-(C<sub>1-20</sub> alkyl)<sub>0-1</sub>-aryl;
- O-(C<sub>1-20</sub> alkyl)<sub>0-1</sub>-heteroaryl;
- 30 -O-(C<sub>1-20</sub> alkyl)<sub>0-1</sub>-heterocyclyl;
- CO-O-C<sub>1-20</sub> alkyl;
- S(O)<sub>0-2</sub>-C<sub>1-20</sub> alkyl;

-S(O)<sub>0-2</sub>-(C<sub>1-20</sub> alkyl)<sub>0-1</sub>-aryl;  
 -S(O)<sub>0-2</sub>-(C<sub>1-20</sub> alkyl)<sub>0-1</sub>-heteroaryl;  
 -S(O)<sub>0-2</sub>-(C<sub>1-20</sub> alkyl)<sub>0-1</sub>-heterocyclyl;  
 -N(R<sub>310</sub>)<sub>2</sub>;  
 5 -NR<sub>310</sub>-CO-O-C<sub>1-20</sub> alkyl;  
 -N<sub>3</sub>;  
 oxo;  
 -halogen;  
 -NO<sub>2</sub>;  
 10 -OH; and  
 -SH; or R<sub>410</sub> is



wherein Y is -N- or -CR-;

R<sub>210</sub> is selected from:

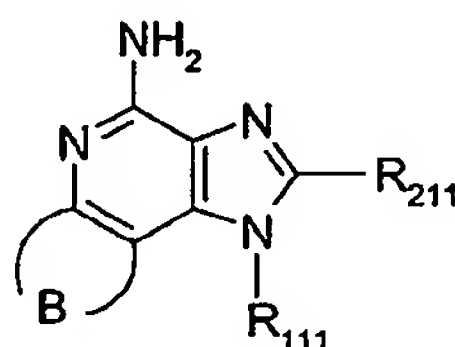
15 -hydrogen;  
 -C<sub>1-10</sub> alkyl;  
 -C<sub>2-10</sub> alkenyl;  
 -aryl;  
 -C<sub>1-10</sub> alkyl-O-C<sub>1-10</sub> alkyl;  
 20 -C<sub>1-10</sub> alkyl-O-C<sub>2-10</sub> alkenyl; and  
 -C<sub>1-10</sub> alkyl or C<sub>2-10</sub> alkenyl substituted by one or more substituents selected  
 from:  
 -OH;  
 -halogen;  
 25 -N(R<sub>310</sub>)<sub>2</sub>;  
 -CO-N(R<sub>310</sub>)<sub>2</sub>;  
 -CO-C<sub>1-10</sub> alkyl;  
 -N<sub>3</sub>;

-aryl;  
 -heteroaryl;  
 -heterocyclyl;  
 -CO-aryl; and  
 -CO-heteroaryl;

5

each  $R_{310}$  is independently selected from hydrogen and  $C_{1-10}$  alkyl; and

each R is independently selected from hydrogen,  $C_{1-10}$  alkyl,  $C_{1-10}$  alkoxy, halogen and trifluoromethyl;



10

XI

wherein

B is  $-NR-C(R)_2-C(R)_2-C(R)_2-$ ;  $-C(R)_2-NR-C(R)_2-C(R)_2-$ ;  
 $-C(R)_2-C(R)_2-NR-C(R)_2-$  or  $-C(R)_2-C(R)_2-C(R)_2-NR-$ ;

$R_{111}$  is selected from:

15

- hydrogen;

$-C_{1-20}$  alkyl or  $C_{2-20}$  alkenyl that is unsubstituted or substituted by one or more substituents selected from:

-aryl;  
 -heteroaryl;  
 -heterocyclyl;  
 -O- $C_{1-20}$  alkyl;  
 -O-( $C_{1-20}$  alkyl) $_{0-1}$ -aryl;  
 -O-( $C_{1-20}$  alkyl) $_{0-1}$ -heteroaryl;  
 -O-( $C_{1-20}$  alkyl) $_{0-1}$ -heterocyclyl;  
 -CO-O- $C_{1-20}$  alkyl;  
 -S(O) $_{0-2}$ - $C_{1-20}$  alkyl;  
 -S(O) $_{0-2}$ -( $C_{1-20}$  alkyl) $_{0-1}$ -aryl;  
 -S(O) $_{0-2}$ -( $C_{1-20}$  alkyl) $_{0-1}$ -heteroaryl;

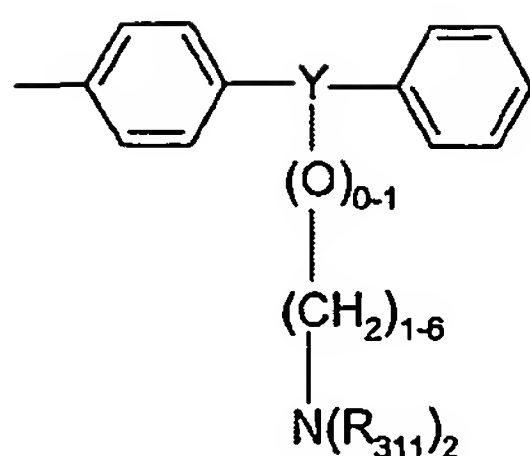
20

25

-S(O)<sub>0-2</sub>-(C<sub>1-20</sub> alkyl)<sub>0-1</sub>-heterocyclyl;  
 -N(R<sub>311</sub>)<sub>2</sub>;  
 -N<sub>3</sub>;  
 oxo;  
 5 -halogen;  
 -NO<sub>2</sub>;  
 -OH; and  
 -SH; and

-C<sub>1-20</sub> alkyl-NR<sub>311</sub>-Q-X-R<sub>411</sub> or -C<sub>2-20</sub> alkenyl-NR<sub>311</sub>-Q-X-R<sub>411</sub> wherein Q is -CO-  
 10 or -SO<sub>2</sub>-; X is a bond, -O- or -NR<sub>311</sub>- and R<sub>411</sub> is aryl; heteroaryl; heterocyclyl; or -C<sub>1-20</sub>  
 alkyl or C<sub>2-20</sub> alkenyl that is unsubstituted or substituted by one or more substituents  
 selected from:

-aryl;  
 -heteroaryl;  
 15 -heterocyclyl;  
 -O-C<sub>1-20</sub> alkyl;  
 -O-(C<sub>1-20</sub> alkyl)<sub>0-1</sub>-aryl;  
 -O-(C<sub>1-20</sub> alkyl)<sub>0-1</sub>-heteroaryl;  
 -O-(C<sub>1-20</sub> alkyl)<sub>0-1</sub>-heterocyclyl;  
 20 -CO-O-C<sub>1-20</sub> alkyl;  
 -S(O)<sub>0-2</sub>-C<sub>1-20</sub> alkyl;  
 -S(O)<sub>0-2</sub>-(C<sub>1-20</sub> alkyl)<sub>0-1</sub>-aryl;  
 -S(O)<sub>0-2</sub>-(C<sub>1-20</sub> alkyl)<sub>0-1</sub>-heteroaryl;  
 -S(O)<sub>0-2</sub>-(C<sub>1-20</sub> alkyl)<sub>0-1</sub>-heterocyclyl;  
 25 -N(R<sub>311</sub>)<sub>2</sub>;  
 -NR<sub>311</sub>-CO-O-C<sub>1-20</sub> alkyl;  
 -N<sub>3</sub>;  
 oxo;  
 -halogen;  
 30 -NO<sub>2</sub>;  
 -OH; and  
 -SH; or R<sub>411</sub> is



wherein Y is  $\text{---N---}$  or  $\text{---CR---}$ ;

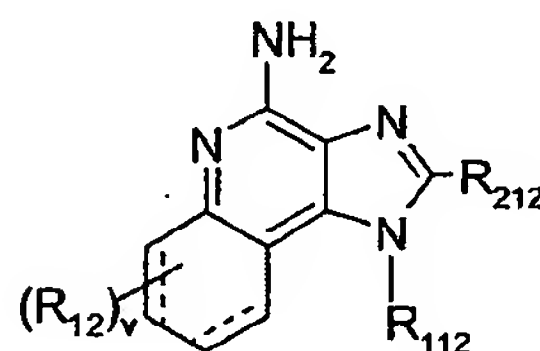
$\text{R}_{211}$  is selected from:

- hydrogen;
- $\text{C}_{1-10}$  alkyl;
- $\text{C}_{2-10}$  alkenyl;
- aryl;
- $\text{C}_{1-10}$  alkyl -O- $\text{C}_{1-10}$ -alkyl;
- $\text{C}_{1-10}$  alkyl-O- $\text{C}_{2-10}$  alkenyl; and
- $\text{C}_{1-10}$  alkyl or  $\text{C}_{2-10}$  alkenyl substituted by one or more substituents selected from:
  - OH;
  - halogen;
  - $\text{N}(\text{R}_{311})_2$ ;
  - CO- $\text{N}(\text{R}_{311})_2$ ;
  - CO- $\text{C}_{1-10}$  alkyl;
  - $\text{N}_3$ ;
  - aryl;
  - heteroaryl;
  - heterocyclyl;
  - CO-aryl; and
  - CO-heteroaryl;

each  $\text{R}_{311}$  is independently selected from hydrogen and  $\text{C}_{1-10}$  alkyl; and

each R is independently selected from hydrogen,  $\text{C}_{1-10}$  alkyl,  $\text{C}_{1-10}$  alkoxy, halogen, and trifluoromethyl; and pharmaceutically acceptable salts thereof.

In another embodiment, the IRM compound can be chosen from 1*H*-imidazo[4,5-*c*]quinolin-4-amines and tetrahydro- 1*H*-imidazo[4,5-*c*]quinolin-4-amines defined by Formulas XII, XIII and XIV below:



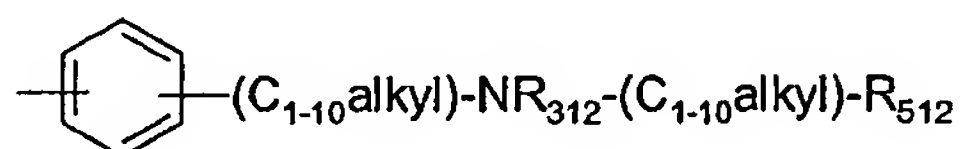
XII

wherein

R<sub>112</sub> is -alkyl-NR<sub>312</sub>-CO-R<sub>412</sub> or -alkenyl-NR<sub>312</sub>-CO- R<sub>412</sub> wherein R<sub>412</sub> is aryl, heteroaryl, alkyl or alkenyl, each of which may be unsubstituted or substituted by one or more substituents selected from:

- alkyl;
- alkenyl;
- alkynyl;
- (alkyl)<sub>0-1</sub>-aryl;
- (alkyl)<sub>0-1</sub>-(substituted aryl);
- (alkyl)<sub>0-1</sub>-heteroaryl;
- (alkyl)<sub>0-1</sub>-(substituted heteroaryl);
- O-alkyl;
- O-(alkyl)<sub>0-1</sub>-aryl;
- O-(alkyl)<sub>0-1</sub>-(substituted aryl);
- O-(alkyl)<sub>0-1</sub>-heteroaryl;
- O-(alkyl)<sub>0-1</sub>-(substituted heteroaryl);
- CO-aryl;
- CO-(substituted aryl);
- CO-heteroaryl;
- CO-(substituted heteroaryl);
- COOH;
- CO-O-alkyl;

- CO-alkyl;  
 -S(O)<sub>0-2</sub>-alkyl;  
 -S(O)<sub>0-2</sub>-(alkyl)<sub>0-1</sub>-aryl;  
 -S(O)<sub>0-2</sub>-(alkyl)<sub>0-1</sub>-(substituted aryl);  
 5 -S(O)<sub>0-2</sub>-(alkyl)<sub>0-1</sub>-heteroaryl;  
 -S(O)<sub>0-2</sub>-(alkyl)<sub>0-1</sub>-(substituted heteroaryl);  
 -P(O)(OR<sub>312</sub>)<sub>2</sub>;  
 -NR<sub>312</sub>-CO-O-alkyl;  
 -N<sub>3</sub>;  
 10 -halogen;  
 -NO<sub>2</sub>;  
 -CN;  
 -haloalkyl;  
 -O-haloalkyl;  
 15 -CO-haloalkyl;  
 -OH;  
 -SH; and in the case that R<sub>412</sub> is alkyl, alkenyl, or heterocyclyl, oxo;  
 or R<sub>412</sub> is



20 wherein R<sub>512</sub> is an aryl, (substituted aryl), heteroaryl, (substituted heteroaryl), heterocyclyl or (substituted heterocyclyl) group;

R<sub>212</sub> is selected from:

- hydrogen;  
 25 -alkyl;  
 -alkenyl;  
 -aryl;  
 -(substituted aryl);  
 -heteroaryl;  
 30 -(substituted heteroaryl);  
 -heterocyclyl;

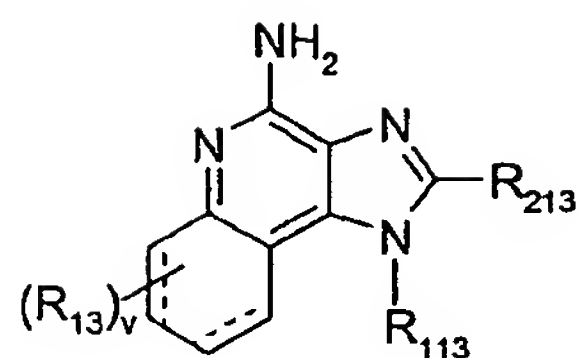
-(substituted heterocyclyl);  
-alkyl-O-alkyl;  
-alkyl-O-alkenyl; and  
-alkyl or alkenyl substituted by one or more substituents selected  
5 from:

-OH;  
-halogen;  
-N(R<sub>312</sub>)<sub>2</sub>;  
-CO-N(R<sub>312</sub>)<sub>2</sub>;  
10 -CO-C<sub>1-10</sub> alkyl;  
-CO-O-C<sub>1-10</sub> alkyl;  
-N<sub>3</sub>;  
-aryl;  
-(substituted aryl);  
15 -heteroaryl;  
-(substituted heteroaryl);  
-heterocyclyl;  
-(substituted heterocyclyl);  
-CO-aryl; and  
20 -CO-heteroaryl;

each R<sub>312</sub> is independently selected from hydrogen; C<sub>1-10</sub> alkyl-heteroaryl; C<sub>1-10</sub> alkyl-(substituted heteroaryl); C<sub>1-10</sub> alkyl-aryl; C<sub>1-10</sub> alkyl-(substituted aryl) and C<sub>1-10</sub> alkyl;

v is 0 to 4;

25 and each R<sub>12</sub> present is independently selected from C<sub>1-10</sub> alkyl, C<sub>1-10</sub> alkoxy, halogen, and trifluoromethyl;



XIII

wherein

$R_{113}$  is -alkyl-NR<sub>313</sub>- SO<sub>2</sub> -X-R<sub>413</sub> or -alkenyl-NR<sub>313</sub>- SO<sub>2</sub> -X-R<sub>413</sub>;

5 X is a bond or -NR<sub>513</sub>-;

$R_{413}$  is aryl, heteroaryl, heterocyclyl, alkyl or alkenyl, each of which may be unsubstituted or substituted by one or more substituents selected from:

- alkyl;
- alkenyl;
- 10 -aryl;
- heteroaryl;
- heterocyclyl;
- substituted cycloalkyl;
- substituted aryl;
- 15 -substituted heteroaryl;
- substituted heterocyclyl;
- O-alkyl;
- O-(alkyl)<sub>0-1</sub>-aryl;
- O-(alkyl)<sub>0-1</sub>-substituted aryl;
- 20 -O-(alkyl)<sub>0-1</sub>-heteroaryl;
- O-(alkyl)<sub>0-1</sub>-substituted heteroaryl;
- O-(alkyl)<sub>0-1</sub>-heterocyclyl;
- O-(alkyl)<sub>0-1</sub>-substituted heterocyclyl;
- COOH;
- 25 -CO-O-alkyl;
- CO-alkyl;
- S(O)<sub>0-2</sub>-alkyl;
- S(O)<sub>0-2</sub>-(alkyl)<sub>0-1</sub>-aryl;
- S(O)<sub>0-2</sub>-(alkyl)<sub>0-1</sub>-substituted aryl;

- 5  
 10  
 15  
 20  
 25  
 30
- S(O)<sub>0-2</sub>-(alkyl)<sub>0-1</sub>-heteroaryl;
  - S(O)<sub>0-2</sub>-(alkyl)<sub>0-1</sub>-substituted heteroaryl;
  - S(O)<sub>0-2</sub>-(alkyl)<sub>0-1</sub>-heterocyclyl;
  - S(O)<sub>0-2</sub>-(alkyl)<sub>0-1</sub>-substituted heterocyclyl;
  - (alkyl)<sub>0-1</sub>-NR<sub>313</sub>R<sub>313</sub>;
  - (alkyl)<sub>0-1</sub>-NR<sub>313</sub>-CO-O-alkyl;
  - (alkyl)<sub>0-1</sub>-NR<sub>313</sub>-CO-alkyl;
  - (alkyl)<sub>0-1</sub>-NR<sub>313</sub>-CO-aryl;
  - (alkyl)<sub>0-1</sub>-NR<sub>313</sub>-CO-substituted aryl;
  - (alkyl)<sub>0-1</sub>-NR<sub>313</sub>-CO-heteroaryl;
  - (alkyl)<sub>0-1</sub>-NR<sub>313</sub>-CO-substituted heteroaryl;
  - N<sub>3</sub>;
  - halogen;
  - haloalkyl;
  - haloalkoxy;
  - CO-haloalkyl;
  - CO-haloalkoxy;
  - NO<sub>2</sub>;
  - CN;
  - OH;
  - SH; and in the case that R<sub>413</sub> is alkyl, alkenyl, or heterocyclyl, oxo;
- R<sub>213</sub> is selected from:
- hydrogen;
  - alkyl;
  - alkenyl;
  - aryl;
  - substituted aryl;
  - heteroaryl;
  - substituted heteroaryl;
  - alkyl-O-alkyl;
  - alkyl-O-alkenyl; and
  - alkyl or alkenyl substituted by one or more substituents selected

from:

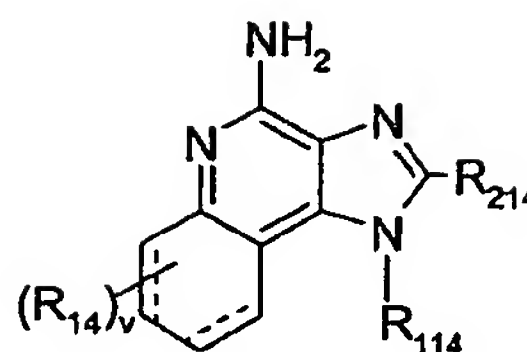
- OH;
- halogen;
- N(R<sub>313</sub>)<sub>2</sub>;
- 5 -CO-N(R<sub>313</sub>)<sub>2</sub>;
- CO-C<sub>1-10</sub> alkyl;
- CO-O-C<sub>1-10</sub> alkyl;
- N<sub>3</sub>;
- aryl;
- 10 -substituted aryl;
- heteroaryl;
- substituted heteroaryl;
- heterocyclyl;
- substituted heterocyclyl;
- 15 -CO-aryl;
- CO-(substituted aryl);
- CO-heteroaryl; and
- CO-(substituted heteroaryl);

each R<sub>313</sub> is independently selected from hydrogen and C<sub>1-10</sub> alkyl; or when X is a  
20 bond R<sub>313</sub> and R<sub>413</sub> can join to form a 3 to 7 membered heterocyclic or substituted  
heterocyclic ring;

R<sub>513</sub> is selected from hydrogen and C<sub>1-10</sub> alkyl, or R<sub>413</sub> and R<sub>513</sub> can combine to  
form a 3 to 7 membered heterocyclic or substituted heterocyclic ring;

v is 0 to 4;

25 and each R<sub>13</sub> present is independently selected from C<sub>1-10</sub> alkyl, C<sub>1-10</sub> alkoxy,  
halogen, and trifluoromethyl;



XIV

wherein

$R_{114}$  is -alkyl-NR<sub>314</sub>-CY-NR<sub>514</sub>-X-R<sub>414</sub> or

5 -alkenyl-NR<sub>314</sub>-CY-NR<sub>514</sub>-X-R<sub>414</sub>

wherein

Y is =O or =S;

X is a bond, -CO- or -SO<sub>2</sub>-;

10  $R_{414}$  is aryl, heteroaryl, heterocyclyl, alkyl or alkenyl, each of which may be unsubstituted or substituted by one or more substituents selected from:

- alkyl;
- alkenyl;
- aryl;
- heteroaryl;
- 15 -heterocyclyl;
- substituted aryl;
- substituted heteroaryl;
- substituted heterocyclyl;
- O-alkyl;
- 20 -O-(alkyl)<sub>0-1</sub>-aryl;
- O-(alkyl)<sub>0-1</sub>-substituted aryl;
- O-(alkyl)<sub>0-1</sub>-heteroaryl;
- O-(alkyl)<sub>0-1</sub>-substituted heteroaryl;
- O-(alkyl)<sub>0-1</sub>-heterocyclyl;
- 25 -O-(alkyl)<sub>0-1</sub>-substituted heterocyclyl;
- COOH;
- CO-O-alkyl;
- CO-alkyl;
- S(O)<sub>0-2</sub>-alkyl;

- S(O)<sub>0-2</sub>-(alkyl)<sub>0-1</sub>-aryl;  
 -S(O)<sub>0-2</sub>-(alkyl)<sub>0-1</sub>-substituted aryl;  
 -S(O)<sub>0-2</sub>-(alkyl)<sub>0-1</sub>-heteroaryl;  
 -S(O)<sub>0-2</sub>-(alkyl)<sub>0-1</sub>-substituted heteroaryl;  
 5 -S(O)<sub>0-2</sub>-(alkyl)<sub>0-1</sub>-heterocyclyl;  
 -S(O)<sub>0-2</sub>-(alkyl)<sub>0-1</sub>-substituted heterocyclyl;  
 -(alkyl)<sub>0-1</sub>-NR<sub>314</sub>R<sub>314</sub>;  
 -(alkyl)<sub>0-1</sub>-NR<sub>314</sub>-CO-O-alkyl;  
 -(alkyl)<sub>0-1</sub>-NR<sub>314</sub>-CO-alkyl;  
 10 -(alkyl)<sub>0-1</sub>-NR<sub>314</sub>-CO-aryl;  
 -(alkyl)<sub>0-1</sub>-NR<sub>314</sub>-CO-substituted aryl;  
 -(alkyl)<sub>0-1</sub>-NR<sub>314</sub>-CO-heteroaryl;  
 -(alkyl)<sub>0-1</sub>-NR<sub>314</sub>-CO-substituted heteroaryl;  
 -N<sub>3</sub>;  
 15 -halogen;  
 -haloalkyl;  
 -haloalkoxy;  
 -CO-haloalkoxy;  
 -NO<sub>2</sub>;  
 20 -CN;  
 -OH;  
 -SH; and, in the case that R<sub>414</sub> is alkyl, alkenyl or heterocyclyl, oxo;  
 with the proviso that when X is a bond R<sub>414</sub> can additionally be hydrogen;  
 R<sub>214</sub> is selected from:  
 25 -hydrogen;  
 -alkyl;  
 -alkenyl;  
 -aryl;  
 -substituted aryl;  
 30 -heteroaryl;  
 -substituted heteroaryl;  
 -alkyl-O-alkyl;

-alkyl-O- alkenyl; and

- alkyl or alkenyl substituted by one or more substituents selected  
from:

- 5                    -OH;  
                    -halogen;  
                    -N(R<sub>314</sub>)<sub>2</sub>;  
                    -CO-N(R<sub>314</sub>)<sub>2</sub>;  
                    -CO-C<sub>1-10</sub> alkyl;  
                    -CO-O-C<sub>1-10</sub> alkyl;  
10                   -N<sub>3</sub>;  
                    -aryl;  
                    -substituted aryl;  
                    -heteroaryl;  
                    -substituted heteroaryl;  
15                   -heterocyclyl;  
                    -substituted heterocyclyl;  
                    -CO-aryl;  
                    -CO-(substituted aryl);  
                    -CO-heteroaryl; and  
20                   -CO-(substituted heteroaryl);

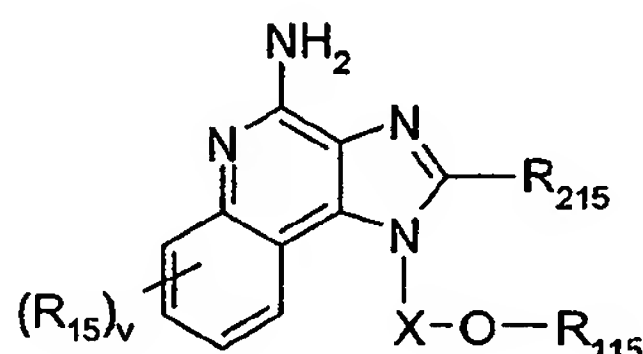
each R<sub>314</sub> is independently selected from hydrogen and C<sub>1-10</sub> alkyl;

R<sub>514</sub> is selected from hydrogen and C<sub>1-10</sub> alkyl, or R<sub>414</sub> and R<sub>514</sub> can combine to  
form a 3 to 7 membered heterocyclic or substituted heterocyclic ring;

v is 0 to 4;

- 25                   and each R<sub>14</sub> present is independently selected from C<sub>1-10</sub> alkyl, C<sub>1-10</sub> alkoxy,  
halogen, and trifluoromethyl;  
and pharmaceutically acceptable salts thereof.

In another embodiment, the IRM compound can be chosen from 1*H*-imidazo[4,5-*c*]quinolin-4-amines and tetrahydro- 1*H*-imidazo[4,5-*c*]quinolin-4-amines defined by Formulas XV, XVI, XVII, XVIII, XIX, XX, XXI, XXII, XXIII, XXIV, XXV, and XXVI below:



XV

wherein: X is  $-\text{CHR}_{515}-$ ,  $-\text{CHR}_{515}\text{-alkyl-}$ , or  $-\text{CHR}_{515}\text{-alkenyl-}$ ;

$\text{R}_{115}$  is selected from:

$-\text{R}_{415}-\text{CR}_{315}-\text{Z}-\text{R}_{615}\text{-alkyl-}$ ;

$-\text{R}_{415}-\text{CR}_{315}-\text{Z}-\text{R}_{615}\text{-alkenyl-}$ ;

$-\text{R}_{415}-\text{CR}_{315}-\text{Z}-\text{R}_{615}\text{-aryl-}$ ;

$-\text{R}_{415}-\text{CR}_{315}-\text{Z}-\text{R}_{615}\text{-heteroaryl-}$ ;

$-\text{R}_{415}-\text{CR}_{315}-\text{Z}-\text{R}_{615}\text{-heterocyclyl-}$ ;

$-\text{R}_{415}-\text{CR}_{315}-\text{Z}-\text{H-}$ ;

$-\text{R}_{415}-\text{NR}_{715}-\text{CR}_{315}-\text{R}_{615}\text{-alkyl-}$ ;

$-\text{R}_{415}-\text{NR}_{715}-\text{CR}_{315}-\text{R}_{615}\text{-alkenyl-}$ ;

$-\text{R}_{415}-\text{NR}_{715}-\text{CR}_{315}-\text{R}_{615}\text{-aryl-}$ ;

$-\text{R}_{415}-\text{NR}_{715}-\text{CR}_{315}-\text{R}_{615}\text{-heteroaryl-}$ ;

$-\text{R}_{415}-\text{NR}_{715}-\text{CR}_{315}-\text{R}_{615}\text{-heterocyclyl-}$ ; and

$-\text{R}_{415}-\text{NR}_{715}-\text{CR}_{315}-\text{R}_{815}$ ;

Z is  $-\text{NR}_{515}-$ ,  $-\text{O}-$ , or  $-\text{S}-$ ;

$\text{R}_{215}$  is selected from:

-hydrogen;

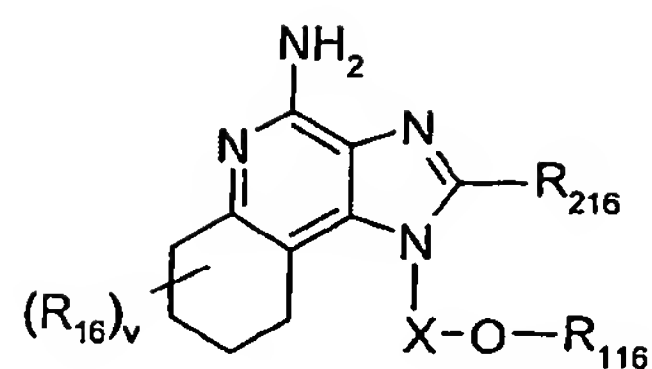
-alkyl;

-alkenyl;

-aryl;

-heteroaryl;

- heterocyclyl;  
 -alkyl-Y-alkyl;  
 -alkyl-Y-alkenyl;  
 -alkyl-Y-aryl; and  
 5 - alkyl or alkenyl substituted by one or more substituents selected  
 from:  
 -OH;  
 -halogen;  
 -N(R<sub>515</sub>)<sub>2</sub>;  
 10 -CO-N(R<sub>515</sub>)<sub>2</sub>;  
 -CO-C<sub>1-10</sub> alkyl;  
 -CO-O-C<sub>1-10</sub> alkyl;  
 -N<sub>3</sub>;  
 -aryl;  
 15 -heteroaryl;  
 -heterocyclyl;  
 -CO-aryl; and  
 -CO-heteroaryl;  
 R<sub>315</sub> is =O or =S;  
 20 R<sub>415</sub> is alkyl or alkenyl, which may be interrupted by one or more  
 -O- groups;  
 each R<sub>515</sub> is independently H or C<sub>1-10</sub> alkyl;  
 R<sub>615</sub> is a bond, alkyl, or alkenyl, which may be interrupted by one or more -  
 O- groups;  
 25 R<sub>715</sub> is H, C<sub>1-10</sub> alkyl, or arylalkyl; or R<sub>415</sub> and R<sub>715</sub> can join together to form  
 a ring;  
 R<sub>815</sub> is H or C<sub>1-10</sub> alkyl; or R<sub>715</sub> and R<sub>815</sub> can join together to form a ring;  
 Y is -O- or -S(O)<sub>0-2</sub>;  
 v is 0 to 4; and  
 30 each R<sub>15</sub> present is independently selected from C<sub>1-10</sub> alkyl, C<sub>1-10</sub> alkoxy,  
 hydroxy, halogen, and trifluoromethyl;



XVI

wherein: X is  $-\text{CHR}_{516}-$ ,  $-\text{CHR}_{516}\text{-alkyl-}$ , or  $-\text{CHR}_{516}\text{-alkenyl-}$ ;

5  $\text{R}_{116}$  is selected from:

- $\text{R}_{416}\text{-CR}_{316}\text{-Z-R}_{616}\text{-alkyl}$ ;
- $\text{R}_{416}\text{-CR}_{316}\text{-Z-R}_{616}\text{-alkenyl}$ ;
- $\text{R}_{416}\text{-CR}_{316}\text{-Z-R}_{616}\text{-aryl}$ ;
- $\text{R}_{416}\text{-CR}_{316}\text{-Z-R}_{616}\text{-heteroaryl}$ ;
- 10 - $\text{R}_{416}\text{-CR}_{316}\text{-Z-R}_{616}\text{-heterocyclyl}$ ;
- $\text{R}_{416}\text{-CR}_{316}\text{-Z-H}$ ;
- $\text{R}_{416}\text{-NR}_{716}\text{-CR}_{316}\text{-R}_{616}\text{-alkyl}$ ;
- $\text{R}_{416}\text{-NR}_{716}\text{-CR}_{316}\text{-R}_{616}\text{-alkenyl}$ ;
- $\text{R}_{416}\text{-NR}_{716}\text{-CR}_{316}\text{-R}_{616}\text{-aryl}$ ;
- 15 - $\text{R}_{416}\text{-NR}_{716}\text{-CR}_{316}\text{-R}_{616}\text{-heteroaryl}$ ;
- $\text{R}_{416}\text{-NR}_{716}\text{-CR}_{316}\text{-R}_{616}\text{-heterocyclyl}$ ; and
- $\text{R}_{416}\text{-NR}_{716}\text{-CR}_{316}\text{-R}_{816}$ ;

Z is  $-\text{NR}_{516}-$ ,  $-\text{O}-$ , or  $-\text{S}-$ ;

$\text{R}_{216}$  is selected from:

- 20 -hydrogen;
- alkyl;
- alkenyl;
- aryl;
- heteroaryl;
- 25 -heterocyclyl;
- alkyl-Y-alkyl;
- alkyl-Y-alkenyl;
- alkyl-Y-aryl; and

- alkyl or alkenyl substituted by one or more substituents selected from:

- OH;
- halogen;
- 5        -N(R<sub>516</sub>)<sub>2</sub>;
- CO-N(R<sub>516</sub>)<sub>2</sub>;
- CO-C<sub>1-10</sub> alkyl;
- CO-O-C<sub>1-10</sub> alkyl;
- N<sub>3</sub>;
- 10        -aryl;
- heteroaryl;
- heterocyclyl;
- CO-aryl; and
- CO-heteroaryl;

15        R<sub>316</sub> is =O or =S;

R<sub>416</sub> is alkyl or alkenyl, which may be interrupted by one or more -O- groups;

each R<sub>516</sub> is independently H or C<sub>1-10</sub> alkyl;

20        R<sub>616</sub> is a bond, alkyl, or alkenyl, which may be interrupted by one or more -O- groups;

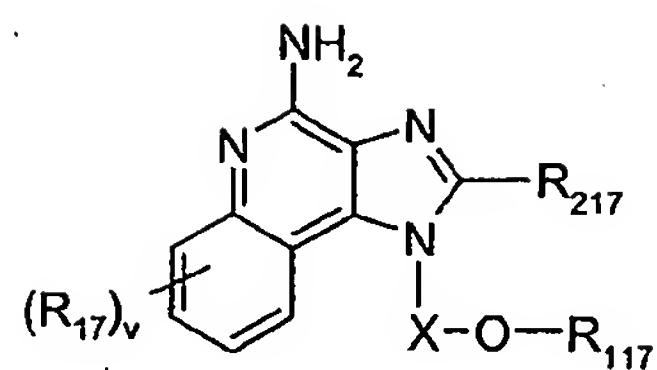
R<sub>716</sub> is H, C<sub>1-10</sub> alkyl, arylalkyl; or R<sub>416</sub> and R<sub>716</sub> can join together to form a ring;

R<sub>816</sub> is H or C<sub>1-10</sub> alkyl; or R<sub>716</sub> and R<sub>816</sub> can join together to form a ring;

Y is -O- or -S(O)<sub>0-2</sub>;

25        v is 0 to 4; and

each R<sub>16</sub> present is independently selected from C<sub>1-10</sub> alkyl, C<sub>1-10</sub> alkoxy, hydroxy, halogen, and trifluoromethyl;



XVII

wherein: X is  $-\text{CHR}_{317}-$ ,  $-\text{CHR}_{317}\text{-alkyl}-$ , or  $-\text{CHR}_{317}\text{-alkenyl}-$ ;

5

$\text{R}_{117}$  is selected from:

-alkenyl;

-aryl; and

$-\text{R}_{417}\text{-aryl}$ ;

$\text{R}_{217}$  is selected from:

10

-hydrogen;

-alkyl;

-alkenyl;

-aryl;

-heteroaryl;

15

-heterocyclyl;

-alkyl-Y-alkyl;

-alkyl-Y-alkenyl;

-alkyl-Y-aryl; and

- alkyl or alkenyl substituted by one or more substituents selected from:

20

-OH;

-halogen;

$-\text{N}(\text{R}_{317})_2$ ;

$-\text{CO}-\text{N}(\text{R}_{317})_2$ ;

25

$-\text{CO}-\text{C}_{1-10}\text{ alkyl}$ ;

$-\text{CO}-\text{O}-\text{C}_{1-10}\text{ alkyl}$ ;

$-\text{N}_3$ ;

-aryl;

-heteroaryl;

-heterocyclyl;  
 -CO-aryl; and  
 -CO-heteroaryl;

$R_{417}$  is alkyl or alkenyl, which may be interrupted by one or more

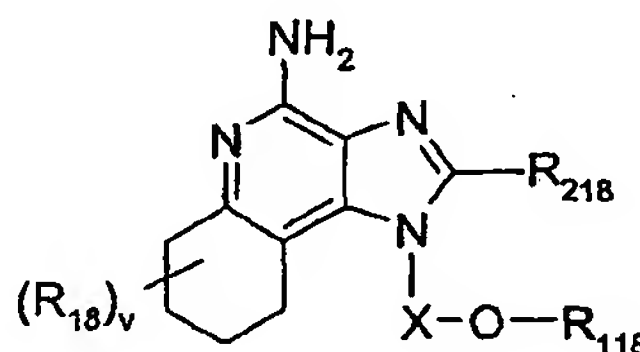
5 -O- groups;

each  $R_{317}$  is independently H or  $C_{1-10}$  alkyl;

each Y is independently -O- or -S(O)<sub>0-2</sub>;

v is 0 to 4; and

each  $R_{17}$  present is independently selected from  $C_{1-10}$  alkyl,  $C_{1-10}$  alkoxy,  
 10 hydroxy, halogen, and trifluoromethyl;



XVIII

15 wherein: X is -CHR<sub>318</sub>-, -CHR<sub>318</sub>-alkyl-, or -CHR<sub>318</sub>-alkenyl-;

$R_{118}$  is selected from:

-aryl;  
 -alkenyl; and  
 -R<sub>418</sub>-aryl;

20  $R_{218}$  is selected from:

-hydrogen;  
 -alkyl;  
 -alkenyl;  
 -aryl;  
 25 -heteroaryl;  
 -heterocyclyl;  
 -alkyl-Y-alkyl;  
 -alkyl-Y-aryl;  
 - alkyl-Y- alkenyl; and

- alkyl or alkenyl substituted by one or more substituents selected from:

- OH;
- halogen;
- N(R<sub>318</sub>)<sub>2</sub>;
- CO-N(R<sub>318</sub>)<sub>2</sub>;
- CO-C<sub>1-10</sub> alkyl;
- CO-O-C<sub>1-10</sub> alkyl;
- N<sub>3</sub>;
- aryl;
- heteroaryl;
- heterocyclyl;
- CO-aryl; and
- CO-heteroaryl;

R<sub>418</sub> is alkyl or alkenyl, which may be interrupted by one or more

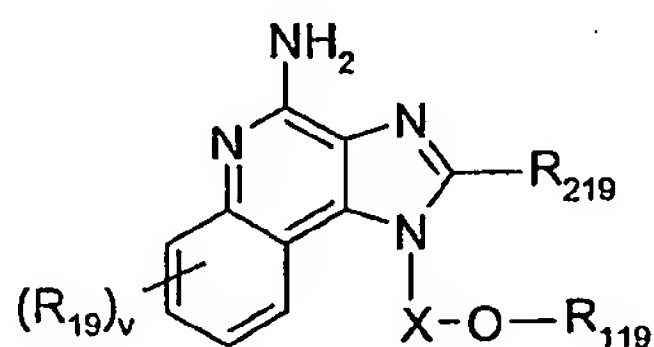
-O- groups;

each R<sub>318</sub> is independently H or C<sub>1-10</sub> alkyl;

each Y is independently -O- or -S(O)<sub>0-2</sub>;

v is 0 to 4; and

each R<sub>18</sub> present is independently selected C<sub>1-10</sub> alkyl, C<sub>1-10</sub> alkoxy, hydroxy, halogen, and trifluoromethyl;



XIX

wherein: X is -CHR<sub>319</sub>-, -CHR<sub>319</sub>-alkyl-, or -CHR<sub>319</sub>-alkenyl-;

R<sub>119</sub> is selected from:

- heteroaryl;
- heterocyclyl;

-R<sub>419</sub>- heteroaryl; and

-R<sub>419</sub>-heterocyclyl;

R<sub>219</sub> is selected from:

-hydrogen;

5

-alkyl;

-alkenyl;

-aryl;

-heteroaryl;

-heterocyclyl;

10

-alkyl-Y-alkyl;

-alkyl-Y- alkenyl;

-alkyl-Y-aryl; and

- alkyl or alkenyl substituted by one or more substituents selected from:

15

-OH;

-halogen;

-N(R<sub>319</sub>)<sub>2</sub>;

-CO-N(R<sub>319</sub>)<sub>2</sub>;

-CO-C<sub>1-10</sub> alkyl;

20

-CO-O-C<sub>1-10</sub> alkyl;

-N<sub>3</sub>;

-aryl;

-heteroaryl;

-heterocyclyl;

25

-CO-aryl; and

-CO-heteroaryl;

R<sub>419</sub> is alkyl or alkenyl, which may be interrupted by one or more

-O- groups;

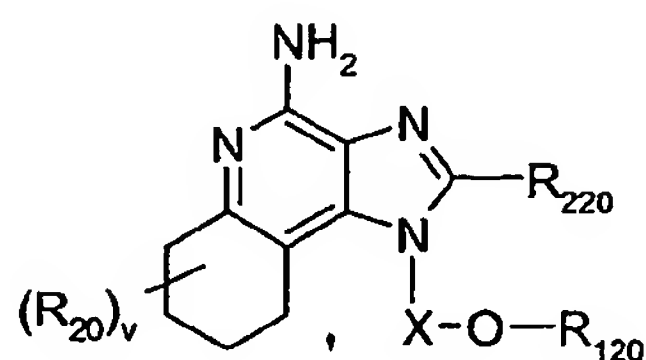
each R<sub>319</sub> is independently H or C<sub>1-10</sub> alkyl;

30

each Y is independently -O- or -S(O)<sub>0-2</sub>;

v is 0 to 4; and

each  $R_{19}$  present is independently selected from  $C_{1-10}$  alkyl,  $C_{1-10}$  alkoxy, hydroxy, halogen, and trifluoromethyl;



XX

wherein: X is  $-\text{CHR}_{320}-$ ,  $-\text{CHR}_{320}\text{-alkyl}-$ , or  $-\text{CHR}_{320}\text{-alkenyl}-$ ;

$R_{120}$  is selected from:

- heteroaryl;
- heterocyclyl;
- $-\text{R}_{420}\text{-heteroaryl}$ ; and
- $-\text{R}_{420}\text{-heterocyclyl}$ ;

$R_{220}$  is selected from:

- hydrogen;
- alkyl;
- alkenyl;
- aryl;
- heteroaryl;
- heterocyclyl;
- alkyl-Y-alkyl;
- alkyl-Y-alkenyl;
- alkyl-Y-aryl; and
- alkyl or alkenyl substituted by one or more substituents selected from:

- OH;
- halogen;
- $-\text{N}(\text{R}_{320})_2$ ;
- $-\text{CO}-\text{N}(\text{R}_{320})_2$ ;
- $-\text{CO}-\text{C}_{1-10}\text{ alkyl}$ ;

-CO-O-C<sub>1-10</sub> alkyl;

-N<sub>3</sub>;

-aryl;

-heteroaryl;

5

-heterocyclyl;

-CO-aryl; and

-CO-heteroaryl;

R<sub>420</sub> is alkyl or alkenyl, which may be interrupted by one or more

-O- groups;

10

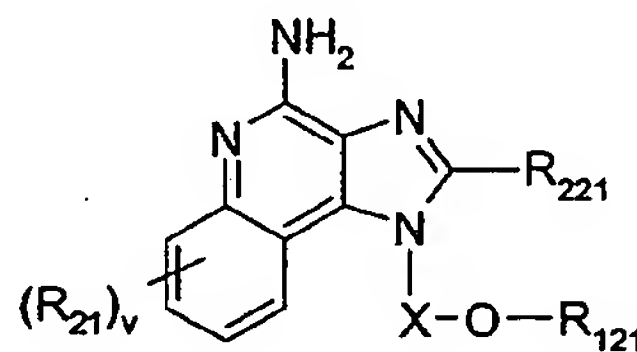
each R<sub>320</sub> is independently H or C<sub>1-10</sub> alkyl;

each Y is independently -O- or -S(O)<sub>0-2</sub>;

v is 0 to 4; and

each R<sub>20</sub> present is independently selected from C<sub>1-10</sub> alkyl, C<sub>1-10</sub> alkoxy, hydroxy, halogen, and trifluoromethyl;

15



XXI

wherein: X is -CHR<sub>521</sub>-, -CHR<sub>521</sub>-alkyl-, or -CHR<sub>521</sub>-alkenyl-;

20

R<sub>121</sub> is selected from:

-R<sub>421</sub>-NR<sub>321</sub>-SO<sub>2</sub>-R<sub>621</sub>-alkyl;

-R<sub>421</sub>-NR<sub>321</sub>-SO<sub>2</sub>-R<sub>621</sub>-alkenyl;

-R<sub>421</sub>-NR<sub>321</sub>-SO<sub>2</sub>-R<sub>621</sub>-aryl;

-R<sub>421</sub>-NR<sub>321</sub>-SO<sub>2</sub>-R<sub>621</sub>-heteroaryl;

25

-R<sub>421</sub>-NR<sub>321</sub>-SO<sub>2</sub>-R<sub>621</sub>-heterocyclyl;

-R<sub>421</sub>-NR<sub>321</sub>-SO<sub>2</sub>-R<sub>721</sub>;

-R<sub>421</sub>-NR<sub>321</sub>-SO<sub>2</sub>-NR<sub>521</sub>-R<sub>621</sub>-alkyl;

-R<sub>421</sub>-NR<sub>321</sub>-SO<sub>2</sub>-NR<sub>521</sub>-R<sub>621</sub>-alkenyl;

-R<sub>421</sub>-NR<sub>321</sub>-SO<sub>2</sub>-NR<sub>521</sub>-R<sub>621</sub>-aryl;

-R<sub>421</sub>-NR<sub>321</sub>-SO<sub>2</sub>-NR<sub>521</sub>-R<sub>621</sub>-heteroaryl;  
 -R<sub>421</sub>-NR<sub>321</sub>-SO<sub>2</sub>-NR<sub>521</sub>-R<sub>621</sub>-heterocyclyl; and  
 -R<sub>421</sub>-NR<sub>321</sub>-SO<sub>2</sub>-NH<sub>2</sub>;

R<sub>221</sub> is selected from:

- 5                    -hydrogen;  
                       -alkyl;  
                       -alkenyl;  
                       -aryl;  
                       -heteroaryl;  
 10                   -heterocyclyl;  
                       -alkyl-Y-alkyl;  
                       -alkyl-Y-alkenyl;  
                       -alkyl-Y-aryl; and  
                       -alkyl or alkenyl substituted by one or more substituents selected  
 15                   from:  
                       -OH;  
                       -halogen;  
                       -N(R<sub>521</sub>)<sub>2</sub>;  
                       -CO-N(R<sub>521</sub>)<sub>2</sub>;  
 20                   -CO-C<sub>1-10</sub> alkyl;  
                       -CO-O-C<sub>1-10</sub> alkyl;  
                       -N<sub>3</sub>;  
                       -aryl;  
                       -heteroaryl;  
 25                   -heterocyclyl;  
                       -CO-aryl; and  
                       -CO-heteroaryl;

Y is -O- or -S(O)<sub>0-2</sub>;

R<sub>321</sub> is H, C<sub>1-10</sub> alkyl, or arylalkyl;

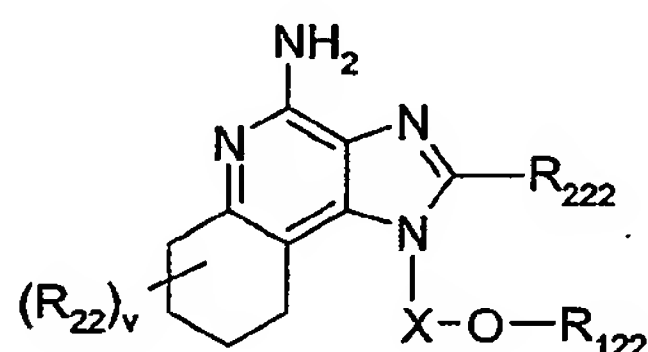
30                   each R<sub>421</sub> is independently alkyl or alkenyl, which may be interrupted by  
                       one or more -O- groups; or R<sub>321</sub> and R<sub>421</sub> can join together to form a ring;  
                       each R<sub>521</sub> is independently H, C<sub>1-10</sub> alkyl, or C<sub>2-10</sub> alkenyl;

$R_{621}$  is a bond, alkyl, or alkenyl, which may be interrupted by one or more -O- groups;

$R_{721}$  is  $C_{1-10}$  alkyl; or  $R_{321}$  and  $R_{721}$  can join together to form a ring;

$v$  is 0 to 4; and

5 each  $R_{21}$  present is independently selected from  $C_{1-10}$  alkyl,  $C_{1-10}$  alkoxy, hydroxy, halogen, and trifluoromethyl;



XXII

10

wherein:  $X$  is  $-\text{CHR}_{522}-$ ,  $-\text{CHR}_{522}\text{-alkyl-}$ , or  $-\text{CHR}_{522}\text{-alkenyl-}$ ;

$R_{122}$  is selected from:

15

$-\text{R}_{422}-\text{NR}_{322}-\text{SO}_2-\text{R}_{622}\text{-alkyl-}$ ;

$-\text{R}_{422}-\text{NR}_{322}-\text{SO}_2-\text{R}_{622}\text{-alkenyl-}$ ;

$-\text{R}_{422}-\text{NR}_{322}-\text{SO}_2-\text{R}_{622}\text{-aryl-}$ ;

$-\text{R}_{422}-\text{NR}_{322}-\text{SO}_2-\text{R}_{622}\text{-heteroaryl-}$ ;

$-\text{R}_{422}-\text{NR}_{322}-\text{SO}_2-\text{R}_{622}\text{-heterocyclyl-}$ ;

$-\text{R}_{422}-\text{NR}_{322}-\text{SO}_2-\text{R}_{722}$ ;

$-\text{R}_{422}-\text{NR}_{322}-\text{SO}_2-\text{NR}_{522}-\text{R}_{622}\text{-alkyl-}$ ;

20

$-\text{R}_{422}-\text{NR}_{322}-\text{SO}_2-\text{NR}_{522}-\text{R}_{622}\text{-alkenyl-}$ ;

$-\text{R}_{422}-\text{NR}_{322}-\text{SO}_2-\text{NR}_{522}-\text{R}_{622}\text{-aryl-}$ ;

$-\text{R}_{422}-\text{NR}_{322}-\text{SO}_2-\text{NR}_{522}-\text{R}_{622}\text{-heteroaryl-}$ ;

$-\text{R}_{422}-\text{NR}_{322}-\text{SO}_2-\text{NR}_{522}-\text{R}_{622}\text{-heterocyclyl-}$ ; and

$-\text{R}_{422}-\text{NR}_{322}-\text{SO}_2-\text{NH}_2$ ;

25

$R_{222}$  is selected from:

-hydrogen;

-alkyl;

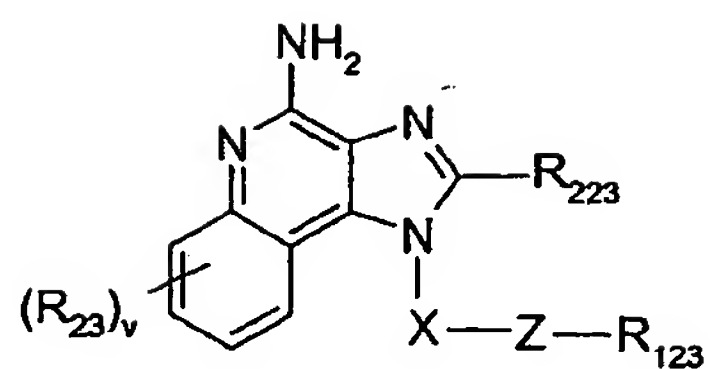
-alkenyl;

-aryl;

-heteroaryl;  
 -heterocyclyl;  
 -alkyl-Y-alkyl;  
 -alkyl-Y-alkenyl;  
 5 -alkyl-Y-aryl; and  
 -alkyl or alkenyl substituted by one or more substituents selected  
 from:

10 -OH;  
 -halogen;  
 -N(R<sub>522</sub>)<sub>2</sub>;  
 -CO-N(R<sub>522</sub>)<sub>2</sub>;  
 -CO-C<sub>1-10</sub> alkyl;  
 -CO-O-C<sub>1-10</sub> alkyl;  
 15 -N<sub>3</sub>;  
 -aryl;  
 -heteroaryl;  
 -heterocyclyl;  
 -CO-aryl; and  
 -CO-heteroaryl;

20 Y is -O- or -S(O)<sub>0-2</sub>;  
 R<sub>322</sub> is H, C<sub>1-10</sub> alkyl, or arylalkyl;  
 each R<sub>422</sub> is independently alkyl or alkenyl, which may be interrupted by  
 one or more -O- groups; or R<sub>322</sub> and R<sub>422</sub> can join together to form a ring;  
 each R<sub>522</sub> is independently H, C<sub>1-10</sub> alkyl, or C<sub>2-10</sub> alkenyl;  
 25 R<sub>622</sub> is a bond, alkyl, or alkenyl, which may be interrupted by one or more -  
 O- groups;  
 R<sub>722</sub> is C<sub>1-10</sub> alkyl; or R<sub>322</sub> and R<sub>722</sub> can join together to form a ring;  
 v is 0 to 4; and  
 each R<sub>22</sub> present is independently selected from C<sub>1-10</sub> alkyl, C<sub>1-10</sub> alkoxy,  
 30 hydroxy, halogen, and trifluoromethyl;



XXIII

wherein: X is  $-\text{CHR}_{323}-$ ,  $-\text{CHR}_{323}\text{-alkyl}-$ , or  $-\text{CHR}_{323}\text{-alkenyl}-$ ;

5 Z is  $-\text{S}-$ ,  $-\text{SO}-$ , or  $-\text{SO}_2-$ ;

$\text{R}_{123}$  is selected from:

- alkyl;
- aryl;
- heteroaryl;
- 10 -heterocyclyl;
- alkenyl;
- $-\text{R}_{423}\text{-aryl}$ ;
- $-\text{R}_{423}\text{-heteroaryl}$ ; and
- $-\text{R}_{423}\text{-heterocyclyl}$ ;

15  $\text{R}_{223}$  is selected from:

- hydrogen;
- alkyl;
- alkenyl;
- aryl;
- 20 -heteroaryl;
- heterocyclyl;
- alkyl-Y-alkyl;
- alkyl-Y-alkenyl;
- alkyl-Y-aryl; and
- 25 -alkyl or alkenyl substituted by one or more substituents selected from:

- OH;
- halogen;
- $-\text{N}(\text{R}_{323})_2$ ;

5

-CO-N(R<sub>323</sub>)<sub>2</sub>;  
 -CO-C<sub>1-10</sub> alkyl;  
 -CO-O-C<sub>1-10</sub> alkyl;  
 -N<sub>3</sub>;  
 -aryl;  
 -heteroaryl;  
 -heterocyclyl;  
 -CO-aryl; and  
 -CO-heteroaryl;

10

each R<sub>323</sub> is independently H or C<sub>1-10</sub> alkyl;

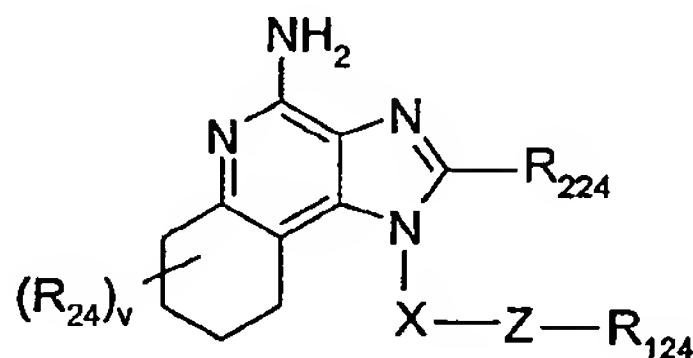
each R<sub>423</sub> is independently alkyl or alkenyl;

each Y is independently -O- or -S(O)<sub>0-2</sub>-;

v is 0 to 4; and

15

each R<sub>23</sub> present is independently selected from C<sub>1-10</sub> alkyl, C<sub>1-10</sub> alkoxy, hydroxy, halogen, and trifluoromethyl;



XXIV

20

wherein:

X is -CHR<sub>324</sub>-, -CHR<sub>324</sub>-alkyl-, or -CHR<sub>324</sub>-alkenyl-;

Z is -S-, -SO-, or -SO<sub>2</sub>-;

R<sub>124</sub> is selected from:

25

-alkyl;  
 -aryl;  
 -heteroaryl;  
 -heterocyclyl;  
 -alkenyl;  
 -R<sub>424</sub>-aryl;  
 -R<sub>424</sub>-heteroaryl; and

-R<sub>424</sub>-heterocyclyl;

R<sub>224</sub> is selected from:

-hydrogen;

-alkyl;

5 -alkenyl;

-aryl;

-heteroaryl;

-heterocyclyl;

-alkyl-Y-alkyl;

10 - alkyl-Y- alkenyl;

-alkyl-Y-aryl; and

- alkyl or alkenyl substituted by one or more substituents selected from:

-OH;

15 -halogen;

-N(R<sub>324</sub>)<sub>2</sub>;

-CO-N(R<sub>324</sub>)<sub>2</sub>;

-CO-C<sub>1-10</sub> alkyl;

-CO-O-C<sub>1-10</sub> alkyl;

20 -N<sub>3</sub>;

-aryl;

-heteroaryl;

-heterocyclyl;

-CO-aryl; and

25 -CO-heteroaryl;

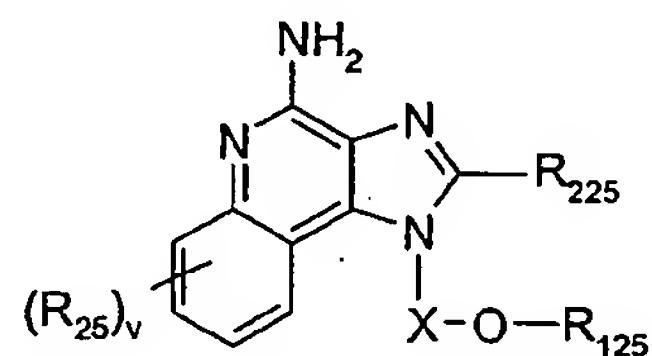
each R<sub>324</sub> is independently H or C<sub>1-10</sub> alkyl;

each R<sub>424</sub> is independently alkyl or alkenyl;

each Y is independently -O- or -S(O)<sub>0-2</sub>;

v is 0 to 4; and

30 each R<sub>24</sub> present is independently selected from C<sub>1-10</sub> alkyl, C<sub>1-10</sub> alkoxy, hydroxy, halogen, and trifluoromethyl;



XXV

wherein: X is  $-\text{CHR}_{525}-$ ,  $-\text{CHR}_{525}\text{-alkyl}-$ , or  $-\text{CHR}_{525}\text{-alkenyl}-$ ;

5

$\text{R}_{125}$  is selected from:

10

- $-\text{R}_{425}\text{-NR}_{825}\text{-CR}_{325}\text{-NR}_{525}\text{-Z-R}_{625}\text{-alkyl};$
- $-\text{R}_{425}\text{-NR}_{825}\text{-CR}_{325}\text{-NR}_{525}\text{-Z-R}_{625}\text{-alkenyl};$
- $-\text{R}_{425}\text{-NR}_{825}\text{-CR}_{325}\text{-NR}_{525}\text{-Z-R}_{625}\text{-aryl};$
- $-\text{R}_{425}\text{-NR}_{825}\text{-CR}_{325}\text{-NR}_{525}\text{-Z-R}_{625}\text{-heteroaryl};$
- $-\text{R}_{425}\text{-NR}_{825}\text{-CR}_{325}\text{-NR}_{525}\text{-Z-R}_{625}\text{-heterocyclyl};$
- $-\text{R}_{425}\text{-NR}_{825}\text{-CR}_{325}\text{-NR}_{525}\text{-R}_{725};$
- $-\text{R}_{425}\text{-NR}_{825}\text{-CR}_{325}\text{-NR}_{925}\text{-Z-R}_{625}\text{-alkyl};$
- $-\text{R}_{425}\text{-NR}_{825}\text{-CR}_{325}\text{-NR}_{925}\text{-Z-R}_{625}\text{-alkenyl};$
- $-\text{R}_{425}\text{-NR}_{825}\text{-CR}_{325}\text{-NR}_{925}\text{-Z-R}_{625}\text{-aryl};$
- $-\text{R}_{425}\text{-NR}_{825}\text{-CR}_{325}\text{-NR}_{925}\text{-Z-R}_{625}\text{-heteroaryl};$  and
- $-\text{R}_{425}\text{-NR}_{825}\text{-CR}_{325}\text{-NR}_{925}\text{-Z-R}_{625}\text{-heterocyclyl};$

15

$\text{R}_{225}$  is selected from:

20

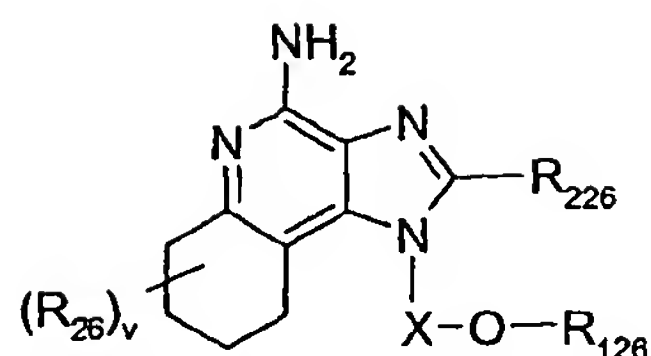
- hydrogen;
- alkyl;
- alkenyl;
- aryl;
- heteroaryl;
- heterocyclyl;
- alkyl-Y-alkyl;
- alkyl-Y-alkenyl;
- alkyl-Y-aryl; and

25

- alkyl or alkenyl substituted by one or more substituents selected from:

-OH;

- 5                    -halogen;  
                     -N(R<sub>525</sub>)<sub>2</sub>;  
                     -CO-N(R<sub>525</sub>)<sub>2</sub>;  
                     -CO-C<sub>1-10</sub> alkyl;  
                     -CO-O-C<sub>1-10</sub> alkyl;  
                     -N<sub>3</sub>;  
                     -aryl;  
                     -heteroaryl;  
                     -heterocyclyl;  
 10                   -CO-aryl; and  
                     -CO-heteroaryl;  
  
                     each R<sub>325</sub> is =O or =S;  
                     each R<sub>425</sub> is independently alkyl or alkenyl, which may be interrupted by  
                     one or more -O- groups;  
 15                   each R<sub>525</sub> is independently H or C<sub>1-10</sub> alkyl;  
                     R<sub>625</sub> is a bond, alkyl, or alkenyl, which may be interrupted by one or more -  
                     O- groups;  
                     R<sub>725</sub> is H or C<sub>1-10</sub> alkyl which may be interrupted by a hetero atom, or R<sub>725</sub>  
                     can join with R<sub>525</sub> to form a ring;  
 20                   R<sub>825</sub> is H, C<sub>1-10</sub> alkyl, or arylalkyl; or R<sub>425</sub> and R<sub>825</sub> can join together to form  
                     a ring;  
                     R<sub>925</sub> is C<sub>1-10</sub> alkyl which can join together with R<sub>825</sub> to form a ring;  
                     each Y is independently -O- or -S(O)<sub>0-2</sub>;  
                     Z is a bond, -CO-, or -SO<sub>2</sub>-;  
 25                   v is 0 to 4; and  
                     each R<sub>25</sub> present is independently selected C<sub>1-10</sub> alkyl, C<sub>1-10</sub> alkoxy,  
                     hydroxy, halogen, and trifluoromethyl;



XXVI

wherein: X is  $-\text{CHR}_{526}-$ ,  $-\text{CHR}_{526}\text{-alkyl-}$ , or  $-\text{CHR}_{526}\text{-alkenyl-}$ ;

5  $\text{R}_{126}$  is selected from:

- $\text{R}_{426}\text{-NR}_{826}\text{-CR}_{326}\text{-NR}_{526}\text{-Z-R}_{626}\text{-alkyl}$ ;
- $\text{R}_{426}\text{-NR}_{826}\text{-CR}_{326}\text{-NR}_{526}\text{-Z-R}_{626}\text{-alkenyl}$ ;
- $\text{R}_{426}\text{-NR}_{826}\text{-CR}_{326}\text{-NR}_{526}\text{-Z-R}_{626}\text{-aryl}$ ;
- $\text{R}_{426}\text{-NR}_{826}\text{-CR}_{326}\text{-NR}_{526}\text{-Z-R}_{626}\text{-heteroaryl}$ ;
- 10 - $\text{R}_{426}\text{-NR}_{826}\text{-CR}_{326}\text{-NR}_{526}\text{-Z-R}_{626}\text{-heterocyclyl}$ ;
- $\text{R}_{426}\text{-NR}_{826}\text{-CR}_{326}\text{-NR}_{526}\text{R}_{726}$ ;
- $\text{R}_{426}\text{-NR}_{826}\text{-CR}_{326}\text{-NR}_{926}\text{-Z-R}_{626}\text{-alkyl}$ ;
- $\text{R}_{426}\text{-NR}_{826}\text{-CR}_{326}\text{-NR}_{926}\text{-Z-R}_{626}\text{-alkenyl}$ ;
- $\text{R}_{426}\text{-NR}_{826}\text{-CR}_{326}\text{-NR}_{926}\text{-Z-R}_{626}\text{-aryl}$ ;
- 15 - $\text{R}_{426}\text{-NR}_{826}\text{-CR}_{326}\text{-NR}_{926}\text{-Z-R}_{626}\text{-heteroaryl}$ ; and
- $\text{R}_{426}\text{-NR}_{826}\text{-CR}_{326}\text{-NR}_{926}\text{-Z-R}_{626}\text{-heterocyclyl}$ ;

$\text{R}_{226}$  is selected from:

- hydrogen;
- alkyl;
- 20 -alkenyl;
- aryl;
- heteroaryl;
- heterocyclyl;
- alkyl-Y-alkyl;
- 25 -alkyl-Y-alkenyl;
- alkyl-Y-aryl; and
- alkyl or alkenyl substituted by one or more substituents selected from:

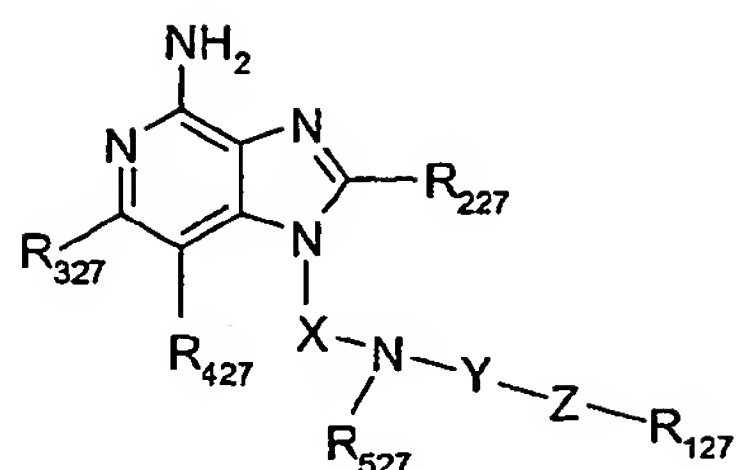
-OH;

5  
 -halogen;  
 -N(R<sub>526</sub>)<sub>2</sub>;  
 -CO-N(R<sub>526</sub>)<sub>2</sub>;  
 -CO-C<sub>1-10</sub> alkyl;  
 -CO-O-C<sub>1-10</sub> alkyl;  
 -N<sub>3</sub>;  
 -aryl;  
 -heteroaryl;  
 -heterocyclyl;  
 10 -CO-aryl; and  
 -CO-heteroaryl;

each R<sub>326</sub> is =O or =S;  
 each R<sub>426</sub> is independently alkyl or alkenyl, which may be interrupted by  
 one or more -O- groups;  
 15 each R<sub>526</sub> is independently H or C<sub>1-10</sub> alkyl;  
 R<sub>626</sub> is a bond, alkyl, or alkenyl, which may be interrupted by one or more -  
 O- groups;  
 R<sub>726</sub> is H or C<sub>1-10</sub> alkyl which may be interrupted by a hetero atom, or R<sub>726</sub>  
 can join with R<sub>526</sub> to form a ring;  
 20 R<sub>826</sub> is H, C<sub>1-10</sub> alkyl, or arylalkyl; or R<sub>426</sub> and R<sub>826</sub> can join together to form  
 a ring;  
 R<sub>926</sub> is C<sub>1-10</sub> alkyl which can join together with R<sub>826</sub> to form a ring;  
 each Y is independently -O- or -S(O)<sub>0-2</sub>;  
 Z is a bond, -CO-, or -SO<sub>2</sub>-;  
 25 v is 0 to 4; and  
 each R<sub>26</sub> present is independently selected from C<sub>1-10</sub> alkyl, C<sub>1-10</sub> alkoxy,  
 hydroxy, halogen, and trifluoromethyl;

and pharmaceutically acceptable salts of any of the foregoing.

30 In another embodiment, the IRM compound can be chosen from 1*H*-imidazo[4,5-  
*c*]pyridin-4-amines defined by Formula XXVII below:



XXVII

wherein

X is alkylene or alkenylene;

Y is  $-\text{CO}-$  or  $-\text{CS}-$ ;

Z is a bond,  $-\text{O}-$ , or  $-\text{S}-$ ;

$\text{R}_{127}$  is aryl, heteroaryl, heterocyclyl, alkyl or alkenyl, each of which may be unsubstituted or substituted by one or more substituents independently selected from:

-alkyl;

-alkenyl;

-aryl;

-heteroaryl;

-heterocyclyl;

-substituted cycloalkyl;

-substituted aryl;

-substituted heteroaryl;

-substituted heterocyclyl;

-O-alkyl;

-O-(alkyl)<sub>0-1</sub>-aryl;

-O-(alkyl)<sub>0-1</sub>-(substituted aryl);

-O-(alkyl)<sub>0-1</sub>-heteroaryl;

-O-(alkyl)<sub>0-1</sub>-(substituted heteroaryl);

-O-(alkyl)<sub>0-1</sub>-heterocyclyl;

-O-(alkyl)<sub>0-1</sub>-(substituted heterocyclyl);

-COOH;

-CO-O-alkyl;

-CO-alkyl;

- S(O)<sub>0-2</sub>-alkyl;  
 -S(O)<sub>0-2</sub>-(alkyl)<sub>0-1</sub>-aryl;  
 -S(O)<sub>0-2</sub>-(alkyl)<sub>0-1</sub>-(substituted aryl);  
 -S(O)<sub>0-2</sub>-(alkyl)<sub>0-1</sub>-heteroaryl;  
 5 -S(O)<sub>0-2</sub>-(alkyl)<sub>0-1</sub>-(substituted heteroaryl);  
 -S(O)<sub>0-2</sub>-(alkyl)<sub>0-1</sub>-heterocyclyl;  
 -S(O)<sub>0-2</sub>-(alkyl)<sub>0-1</sub>-(substituted heterocyclyl);  
 -(alkyl)<sub>0-1</sub>-N(R<sub>627</sub>)<sub>2</sub>;  
 -(alkyl)<sub>0-1</sub>-NR<sub>627</sub>-CO-O-alkyl;  
 10 -(alkyl)<sub>0-1</sub>-NR<sub>627</sub>-CO-alkyl;  
 -(alkyl)<sub>0-1</sub>-NR<sub>627</sub>-CO-aryl;  
 -(alkyl)<sub>0-1</sub>-NR<sub>627</sub>-CO-(substituted aryl);  
 -(alkyl)<sub>0-1</sub>-NR<sub>627</sub>-CO-heteroaryl;  
 -(alkyl)<sub>0-1</sub>-NR<sub>627</sub>-CO-(substituted heteroaryl);  
 15 -N<sub>3</sub>;  
 -halogen;  
 -haloalkyl;  
 -haloalkoxy;  
 -CO-haloalkyl;  
 20 -CO-haloalkoxy;  
 -NO<sub>2</sub>;  
 -CN;  
 -OH;  
 -SH; and in the case of alkyl, alkenyl, and heterocyclyl, oxo;  
 25 R<sub>227</sub> is selected from:  
 -hydrogen;  
 -alkyl;  
 -alkenyl;  
 -aryl;  
 30 -substituted aryl;  
 -heteroaryl;  
 -substituted heteroaryl;

- 5                   -alkyl-O-alkyl;  
                  -alkyl-S-alkyl;  
                  -alkyl-O-aryl;  
                  -alkyl-S-aryl;  
                  -alkyl-O- alkenyl;  
                  -alkyl-S- alkenyl; and  
                  -alkyl or alkenyl substituted by one or more substituents selected  
                  from:  
10                   -OH;  
                  -halogen;  
                  -N(R<sub>627</sub>)<sub>2</sub>;  
                  -CO-N(R<sub>627</sub>)<sub>2</sub>;  
                  -CS-N(R<sub>627</sub>)<sub>2</sub>;  
                  -SO<sub>2</sub>-N(R<sub>627</sub>)<sub>2</sub>;  
15                   -NR<sub>627</sub>-CO-C<sub>1-10</sub> alkyl;  
                  -NR<sub>627</sub>-CS-C<sub>1-10</sub> alkyl;  
                  -NR<sub>627</sub>-SO<sub>2</sub>-C<sub>1-10</sub> alkyl;  
                  -CO-C<sub>1-10</sub> alkyl;  
                  -CO-O-C<sub>1-10</sub> alkyl;  
20                   -N<sub>3</sub>;  
                  -aryl;  
                  -substituted aryl;  
                  -heteroaryl;  
                  -substituted heteroaryl;  
25                   -heterocyclyl;  
                  -substituted heterocyclyl;  
                  -CO-aryl;  
                  -CO-(substituted aryl);  
                  -CO-heteroaryl; and  
30                   -CO-(substituted heteroaryl);

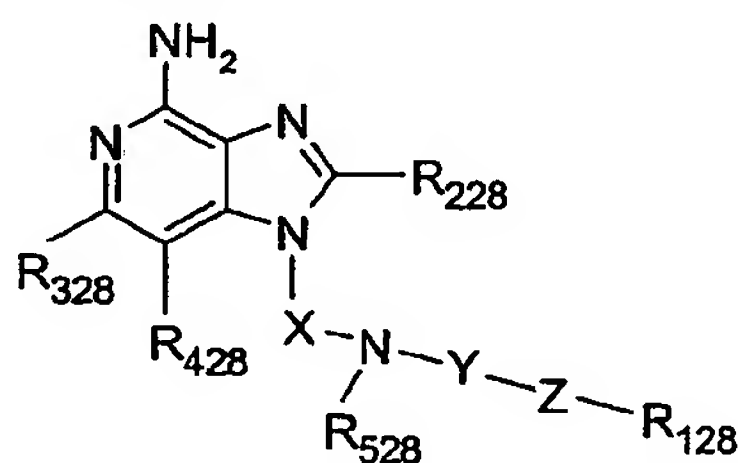
R<sub>327</sub> and R<sub>427</sub> are independently selected from hydrogen, alkyl, alkenyl, halogen, alkoxy, amino, alkylamino, dialkylamino, and alkylthio;

$R_{527}$  is H or  $C_{1-10}$  alkyl, or  $R_{527}$  can join with X to form a ring that contains one or two heteroatoms; or when  $R_{127}$  is alkyl,  $R_{527}$  and  $R_{127}$  can join to form a ring;

each  $R_{627}$  is independently H or  $C_{1-10}$ alkyl;

5 and pharmaceutically acceptable salts thereof.

In another embodiment, the IRM compound can be chosen from 1*H*-imidazo[4,5-*c*]pyridin-4-amines defined by Formula XXVIII below:



XXVIII

10

wherein

X is alkylene or alkenylene;

Y is  $-SO_2-$ ;

Z is a bond or  $-NR_{628}-$ ;

$R_{128}$  is aryl, heteroaryl, heterocyclyl, alkyl or

15

alkenyl, each of which may be unsubstituted or substituted by one or more substituents independently selected from:

-alkyl;

-alkenyl;

-aryl;

20

-heteroaryl;

-heterocyclyl;

-substituted cycloalkyl;

-substituted aryl;

-substituted heteroaryl;

25

-substituted heterocyclyl;

-O-alkyl;

-O-(alkyl)<sub>0-1</sub>-aryl;

-O-(alkyl)<sub>0-1</sub>-(substituted aryl);

- 5
- O-(alkyl)<sub>0-1</sub>-heteroaryl;
  - O-(alkyl)<sub>0-1</sub>-(substituted heteroaryl);
  - O-(alkyl)<sub>0-1</sub>-heterocyclyl;
  - O-(alkyl)<sub>0-1</sub>-(substituted heterocyclyl);
  - COOH;
  - CO-O-alkyl;
  - CO-alkyl;
  - S(O)<sub>0-2</sub>-alkyl;
  - S(O)<sub>0-2</sub>-(alkyl)<sub>0-1</sub>-aryl;
  - 10 -S(O)<sub>0-2</sub>-(alkyl)<sub>0-1</sub>-(substituted aryl);
  - S(O)<sub>0-2</sub>-(alkyl)<sub>0-1</sub>-heteroaryl;
  - S(O)<sub>0-2</sub>-(alkyl)<sub>0-1</sub>-(substituted heteroaryl);
  - S(O)<sub>0-2</sub>-(alkyl)<sub>0-1</sub>-heterocyclyl;
  - S(O)<sub>0-2</sub>-(alkyl)<sub>0-1</sub>-(substituted heterocyclyl);
  - 15 -(alkyl)<sub>0-1</sub>-N(R<sub>628</sub>)<sub>2</sub>;
  - (alkyl)<sub>0-1</sub>-NR<sub>628</sub>-CO-O-alkyl;
  - (alkyl)<sub>0-1</sub>-NR<sub>628</sub>-CO-alkyl;
  - (alkyl)<sub>0-1</sub>-NR<sub>628</sub>-CO-aryl;
  - (alkyl)<sub>0-1</sub>-NR<sub>628</sub>-CO-(substituted aryl);
  - 20 -(alkyl)<sub>0-1</sub>-NR<sub>628</sub>-CO-heteroaryl;
  - (alkyl)<sub>0-1</sub>-NR<sub>628</sub>-CO-(substituted heteroaryl);
  - N<sub>3</sub>;
  - halogen;
  - haloalkyl;
  - 25 -haloalkoxy;
  - CO-haloalkyl;
  - CO-haloalkoxy;
  - NO<sub>2</sub>;
  - CN;
  - 30 -OH;
  - SH; and in the case of alkyl, alkenyl, and heterocyclyl, oxo;

R<sub>228</sub> is selected from:

- 5                    -hydrogen;  
                    -alkyl;  
                    -alkenyl;  
                    -aryl;  
                    -substituted aryl;  
                    -heteroaryl;  
                    -substituted heteroaryl;  
                    -alkyl-O-alkyl;  
                    -alkyl-S-alkyl;  
10                   -alkyl-O-aryl;  
                    -alkyl-S-aryl;  
                    -alkyl-O- alkenyl;  
                    -alkyl-S- alkenyl; and  
                    -alkyl or alkenyl substituted by one or more substituents selected  
15                   from:  
                    -OH;  
                    -halogen;  
                    -N(R<sub>628</sub>)<sub>2</sub>;  
                    -CO-N(R<sub>628</sub>)<sub>2</sub>;  
20                   -CS-N(R<sub>628</sub>)<sub>2</sub>;  
                    -SO<sub>2</sub>-N(R<sub>628</sub>)<sub>2</sub>;  
                    -NR<sub>628</sub>-CO-C<sub>1-10</sub> alkyl;  
                    -NR<sub>628</sub>-CS-C<sub>1-10</sub> alkyl;  
                    -NR<sub>628</sub>-SO<sub>2</sub>-C<sub>1-10</sub> alkyl;  
25                   -CO-C<sub>1-10</sub> alkyl;  
                    -CO-O-C<sub>1-10</sub> alkyl;  
                    -N<sub>3</sub>;  
                    -aryl;  
                    -substituted aryl;  
30                   -heteroaryl;  
                    -substituted heteroaryl;  
                    -heterocyclyl;

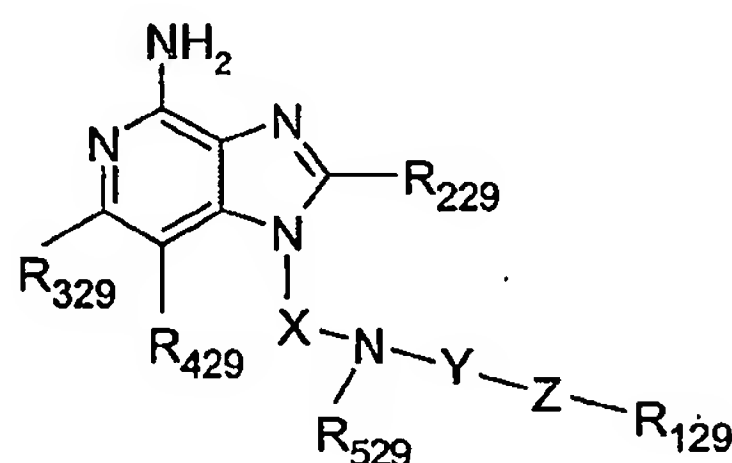
-substituted heterocyclyl;  
 -CO-aryl;  
 -CO-(substituted aryl);  
 -CO-heteroaryl; and  
 -CO-(substituted heteroaryl);

$R_{328}$  and  $R_{428}$  are independently selected from hydrogen, alkyl, alkenyl, halogen, alkoxy, amino, alkylamino, dialkylamino, and alkylthio;

$R_{528}$  is H or  $C_{1-10}$  alkyl, or  $R_{528}$  can join with X to form a ring; or when  $R_{128}$  is alkyl,  $R_{528}$  and  $R_{128}$  can join to form a ring;

each  $R_{628}$  is independently H or  $C_{1-10}$ alkyl;  
 and pharmaceutically acceptable salts thereof.

In another embodiment, the IRM compound can be chosen from 1*H*-imidazo[4,5-*c*]pyridin-4-amines defined by Formula XXIX below:



XXIX

wherein X is alkylene or alkenylene;

Y is -CO- or -CS;

Z is -NR<sub>629</sub>-, -NR<sub>629</sub>-CO-, -NR<sub>629</sub>-SO<sub>2</sub>-, or -NR<sub>729</sub>-;

$R_{129}$  is aryl, heteroaryl, heterocyclyl, alkyl or alkenyl, each of which may be unsubstituted or substituted by one or more substituents independently selected from:

-alkyl;  
 -alkenyl;  
 -aryl;  
 -heteroaryl;  
 -heterocyclyl;  
 -substituted cycloalkyl;

- substituted aryl;
- substituted heteroaryl;
- substituted heterocyclyl;
- O-alkyl;
- 5 -O-(alkyl)<sub>0-1</sub>-aryl;
- O-(alkyl)<sub>0-1</sub>-(substituted aryl);
- O-(alkyl)<sub>0-1</sub>-heteroaryl;
- O-(alkyl)<sub>0-1</sub>-(substituted heteroaryl);
- O-(alkyl)<sub>0-1</sub>-heterocyclyl;
- 10 -O-(alkyl)<sub>0-1</sub>-(substituted heterocyclyl);
- COOH;
- CO-O-alkyl;
- CO-alkyl;
- S(O)<sub>0-2</sub>-alkyl;
- 15 -S(O)<sub>0-2</sub>-(alkyl)<sub>0-1</sub>-aryl;
- S(O)<sub>0-2</sub>-(alkyl)<sub>0-1</sub>-(substituted aryl);
- S(O)<sub>0-2</sub>-(alkyl)<sub>0-1</sub>-heteroaryl;
- S(O)<sub>0-2</sub>-(alkyl)<sub>0-1</sub>-(substituted heteroaryl);
- S(O)<sub>0-2</sub>-(alkyl)<sub>0-1</sub>-heterocyclyl;
- 20 -S(O)<sub>0-2</sub>-(alkyl)<sub>0-1</sub>-(substituted heterocyclyl);
- (alkyl)<sub>0-1</sub>-N(R<sub>629</sub>)<sub>2</sub>;
- (alkyl)<sub>0-1</sub>-NR<sub>629</sub>-CO-O-alkyl;
- (alkyl)<sub>0-1</sub>-NR<sub>629</sub>-CO-alkyl;
- (alkyl)<sub>0-1</sub>-NR<sub>629</sub>-CO-aryl;
- 25 -(alkyl)<sub>0-1</sub>-NR<sub>629</sub>-CO-(substituted aryl);
- (alkyl)<sub>0-1</sub>-NR<sub>629</sub>-CO-heteroaryl;
- (alkyl)<sub>0-1</sub>-NR<sub>629</sub>-CO-(substituted heteroaryl);
- P(O)(O-alkyl)<sub>2</sub>;
- N<sub>3</sub>;
- 30 -halogen;
- haloalkyl;
- haloalkoxy;

5

-CO-haloalkyl;  
-CO-haloalkoxy;  
-NO<sub>2</sub>;  
-CN;  
-OH;  
-SH; and in the case of alkyl, alkenyl, and heterocyclyl, oxo;

R<sub>229</sub> is selected from:

10

-hydrogen;  
-alkyl;  
-alkenyl;  
-aryl;  
-substituted aryl;  
-heteroaryl;  
-substituted heteroaryl;  
-alkyl-O-alkyl;  
-alkyl-S-alkyl;  
-alkyl-O-aryl;  
-alkyl-S-aryl;  
-alkyl-O- alkenyl;  
-alkyl-S- alkenyl; and

15

20

-alkyl or alkenyl substituted by one or more substituents selected from:

25

30

-OH;  
-halogen;  
-N(R<sub>629</sub>)<sub>2</sub>;  
-CO-N(R<sub>629</sub>)<sub>2</sub>;  
-CS-N(R<sub>629</sub>)<sub>2</sub>;  
-SO<sub>2</sub>-N(R<sub>629</sub>)<sub>2</sub>;  
-NR<sub>629</sub>-CO-C<sub>1-10</sub> alkyl;  
-NR<sub>629</sub>-CS-C<sub>1-10</sub> alkyl;  
-NR<sub>629</sub>-SO<sub>2</sub>-C<sub>1-10</sub> alkyl;  
-CO-C<sub>1-10</sub> alkyl;

-CO-O-C<sub>1-10</sub> alkyl;  
 -N<sub>3</sub>;  
 -aryl;  
 -substituted aryl;  
 -heteroaryl;  
 -substituted heteroaryl;  
 -heterocyclyl;  
 -substituted heterocyclyl;  
 -CO-aryl;  
 -CO-(substituted aryl);  
 -CO-heteroaryl; and  
 -CO-(substituted heteroaryl);

R<sub>329</sub> and R<sub>429</sub> are independently selected from hydrogen, alkyl, alkenyl, halogen, alkoxy, amino, alkylamino, dialkylamino, and alkylthio;

R<sub>529</sub> is H or C<sub>1-10</sub> alkyl, or R<sub>529</sub> can join with X to form a ring that contains one or two heteroatoms;

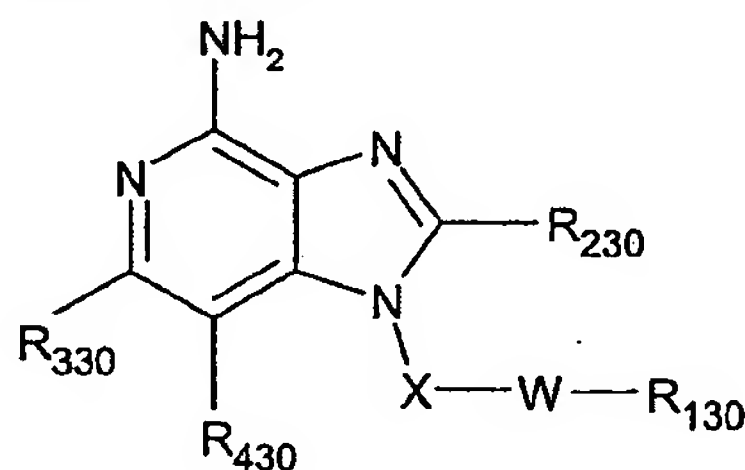
each R<sub>629</sub> is independently H or C<sub>1-10</sub>alkyl;

R<sub>729</sub> is H or C<sub>1-10</sub> alkyl which may be interrupted by a heteroatom; or when

R<sub>129</sub> is alkyl, R<sub>729</sub> and R<sub>129</sub> can join to form a ring;

and pharmaceutically acceptable salts thereof.

In another embodiment, the IRM compound can be chosen from 1-position ether or thioether substituted 1*H*-imidazo[4,5-*c*]pyridin-4-amines defined by Formula XXX below:



XXX

wherein:

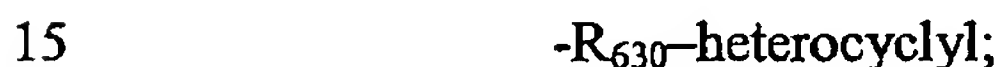
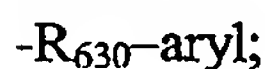
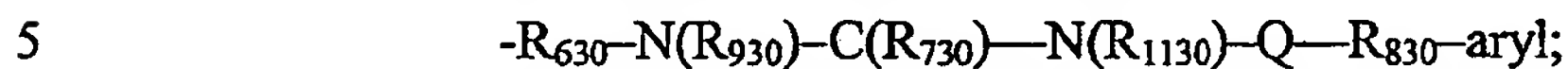
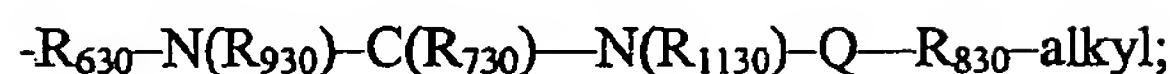
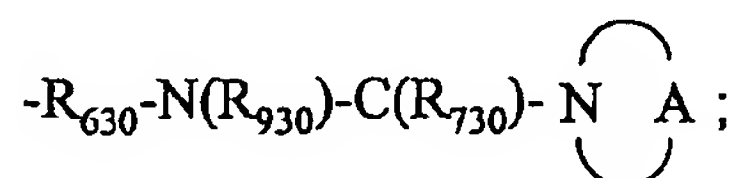
X is -CH(R<sub>530</sub>)-, -CH(R<sub>530</sub>)-alkylene-, -CH(R<sub>530</sub>)-alkenylene-,  
 or CH(R<sub>530</sub>)-alkylene-Y-alkylene-;

Y is  $-O-$ , or  $-S(O)_{0-2}-$ ;

$-W-R_{130}$  is selected from  $-O-R_{130-1-5}$  and  $-S(O)_{0-2}-R_{130-6}$ ;

$R_{130-1-5}$  is selected from

- $R_{630}-C(R_{730})-Z-R_{830}-alkyl$ ;
- 5      - $R_{630}-C(R_{730})-Z-R_{830}-alkenyl$ ;
- $R_{630}-C(R_{730})-Z-R_{830}-aryl$ ;
- $R_{630}-C(R_{730})-Z-R_{830}-heteroaryl$ ;
- $R_{630}-C(R_{730})-Z-R_{830}-heterocyclyl$ ;
- $R_{630}-C(R_{730})-Z-H$ ;
- 10     - $R_{630}-N(R_{930})-C(R_{730})-R_{830}-alkyl$ ;
- $R_{630}-N(R_{930})-C(R_{730})-R_{830}-alkenyl$ ;
- $R_{630}-N(R_{930})-C(R_{730})-R_{830}-aryl$ ;
- $R_{630}-N(R_{930})-C(R_{730})-R_{830}-heteroaryl$ ;
- $R_{630}-N(R_{930})-C(R_{730})-R_{830}-heterocyclyl$ ;
- 15     - $R_{630}-N(R_{930})-C(R_{730})-R_{1030}$ ;
- $R_{630}-N(R_{930})-SO_2-R_{830}-alkyl$ ;
- $R_{630}-N(R_{930})-SO_2-R_{830}-alkenyl$ ;
- $R_{630}-N(R_{930})-SO_2-R_{830}-aryl$ ;
- $R_{630}-N(R_{930})-SO_2-R_{830}-heteroaryl$ ;
- 20     - $R_{630}-N(R_{930})-SO_2-R_{830}-heterocyclyl$ ;
- $R_{630}-N(R_{930})-SO_2-R_{1030}$ ;
- $R_{630}-N(R_{930})-SO_2-N(R_{530})-R_{830}-alkyl$ ;
- $R_{630}-N(R_{930})-SO_2-N(R_{530})-R_{830}-alkenyl$ ;
- $R_{630}-N(R_{930})-SO_2-N(R_{530})-R_{830}-aryl$ ;
- 25     - $R_{630}-N(R_{930})-SO_2-N(R_{530})-R_{830}-heteroaryl$ ;
- $R_{630}-N(R_{930})-SO_2-N(R_{530})-R_{830}-heterocyclyl$ ;
- $R_{630}-N(R_{930})-SO_2-NH_2$ ;
- $R_{630}-N(R_{930})-C(R_{730})-N(R_{530})-Q-R_{830}-alkyl$ ;
- $R_{630}-N(R_{930})-C(R_{730})-N(R_{530})-Q-R_{830}-alkenyl$ ;
- 30     - $R_{630}-N(R_{930})-C(R_{730})-N(R_{530})-Q-R_{830}-aryl$ ;
- $R_{630}-N(R_{930})-C(R_{730})-N(R_{530})-Q-R_{830}-heteroaryl$ ;
- $R_{630}-N(R_{930})-C(R_{730})-N(R_{530})-Q-R_{830}-heterocyclyl$ ;

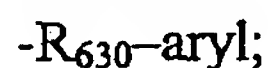


Z is  $-N(R_{530})-$ ,  $-O-$ , or  $-S-$ ;

Q is a bond,  $-\text{CO}-$ , or  $-\text{SO}_2-$ ;

A represents the atoms necessary to provide a 5- or 6-membered heterocyclic or heteroaromatic ring that contains up to three heteroatoms;

20  $R_{130-6}$  is selected from:



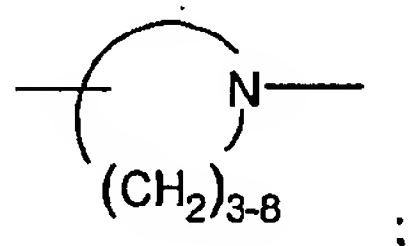
each  $R_{530}$  is independently hydrogen,  $C_{1-10}$  alkyl, or  $C_{2-10}$  alkenyl;

30  $R_{630}$  is alkylene, alkenylene, or alkynylene, which may be interrupted by one or more  $-O-$  groups;

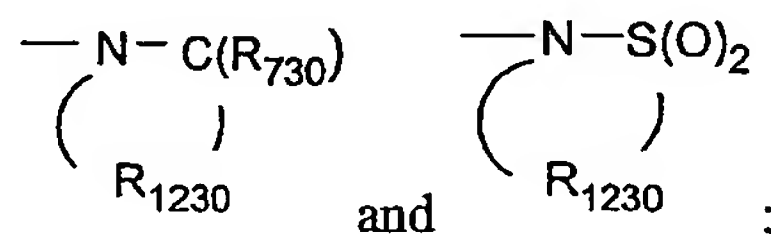
R<sub>730</sub> is =O or =S;

R<sub>830</sub> is a bond, alkylene, alkenylene, or alkynylene, which may be interrupted by one or more -O- groups;

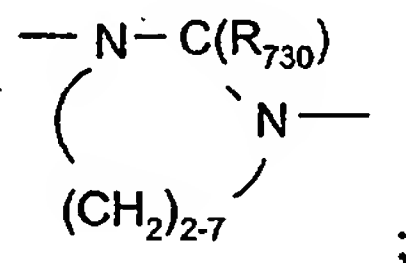
R<sub>930</sub> is hydrogen, C<sub>1-10</sub> alkyl, or arylalkyl; or R<sub>930</sub> can join together with any carbon  
5 atom of R<sub>630</sub> to form a ring of the formula



R<sub>1030</sub> is hydrogen or C<sub>1-10</sub> alkyl; or R<sub>930</sub> and R<sub>1030</sub> can join together to form a ring selected from



10 R<sub>1130</sub> is C<sub>1-10</sub> alkyl; or R<sub>930</sub> and R<sub>1130</sub> can join together to form a ring having the structure



R<sub>1230</sub> is C<sub>2-7</sub> alkylene which is straight chain or branched, wherein the branching does not prevent formation of the ring; and

15             $R_{230}$ ,  $R_{330}$  and  $R_{430}$  are independently selected from hydrogen and non-interfering substituents;

and pharmaceutically acceptable salts thereof.

**Illustrative non-interfering R<sub>230</sub> substituents include:**

-alkyl;

**-alkenyl;**

**-aryl;**

-heteroaryl;

**-heterocyclyl;**

-alkylene-Y-alkyl;

25 -alkylene-Y- alkenyl;

-alkylene-Y-aryl; and

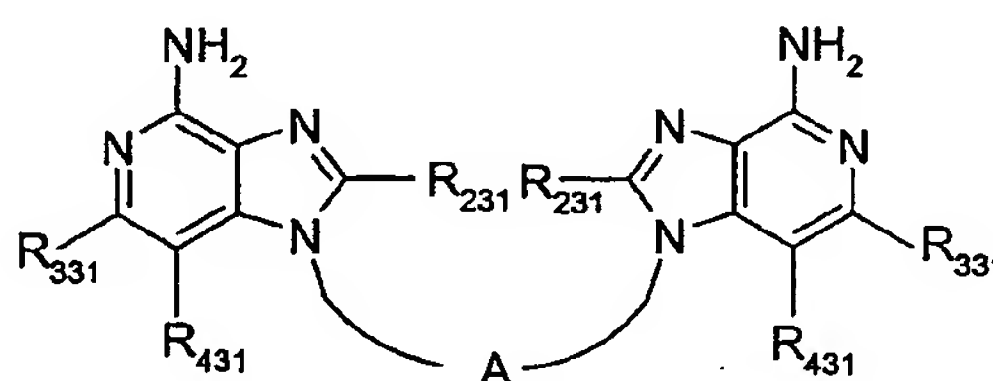
- alkyl or alkenyl substituted by one or more substituents selected from the group consisting of:

- OH;
- halogen;
- N(R<sub>530</sub>)<sub>2</sub>;
- C(O)-C<sub>1-10</sub> alkyl;
- C(O)-O-C<sub>1-10</sub> alkyl;
- N<sub>3</sub>;
- aryl;
- heteroaryl;
- heterocyclyl;
- C(O)-aryl; and
- C(O)-heteroaryl.

Illustrative non-interfering R<sub>330</sub> and R<sub>430</sub> substituents include:

C<sub>1-10</sub> alkyl, C<sub>2-10</sub> alkenyl, C<sub>2-10</sub> alkynyl, C<sub>1-10</sub> alkoxy, C<sub>1-10</sub> alkylthio, amino, alkylamino, dialkylamino, halogen, and nitro.

In another embodiment, the IRM compound can be chosen from 1*H*-imidazo dimers of the formula (XXXI):



XXXI

wherein:

A is a divalent linking group selected from the group consisting of:

- straight or branched chain C<sub>4-20</sub> alkylene;
- straight or branched chain C<sub>4-20</sub> alkenylene;
- straight or branched chain C<sub>4-20</sub> alkynylene; and
- Z-Y-W-Y-Z-;

each Z is independently selected from the group consisting of:

- straight or branched chain C<sub>2-20</sub> alkylene;

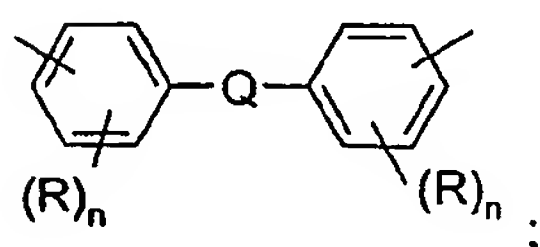
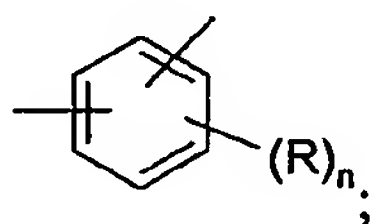
straight or branched chain C<sub>4-20</sub> alkenylene; and  
 straight or branched chain C<sub>4-20</sub> alkynylene;  
 any of which may be optionally interrupted by -O-, -N(R<sub>531</sub>)-, or  
 -S(O)<sub>2</sub>-;

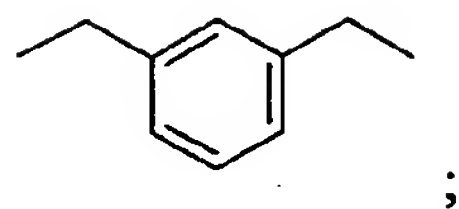
5 each Y is independently selected from the group consisting of:

a bond;  
 -N(R<sub>531</sub>)C(O)-;  
 -C(O)N(R<sub>531</sub>)-;  
 -N(R<sub>531</sub>)C(O)N(R<sub>531</sub>)-;  
 10 -N(R<sub>531</sub>)S(O)<sub>2</sub>-;  
 -S(O)<sub>2</sub>N(R<sub>531</sub>)-;  
 -OC(O)O-;  
 -OC(O)-;  
 -C(O)O-;  
 15 -N(R<sub>531</sub>)C(O)O-; and  
 -OC(O)N(R<sub>531</sub>)-;

W is selected from the group consisting of:

straight or branched chain C<sub>2-20</sub> alkylene;  
 straight or branched chain C<sub>2-20</sub> alkenylene;  
 20 straight or branched chain C<sub>4-20</sub> alkynylene;  
 straight or branched chain perfluoro C<sub>2-20</sub> alkylene;  
 C<sub>1-4</sub> alkylene-O-C<sub>1-4</sub> alkylene;  
 -C(O)-;  
 -S(O)<sub>2</sub>-;  
 25 -OC(O)O-;  
 -N(R<sub>531</sub>)C(O)N(R<sub>531</sub>)-;





1,5-naphthylene;

2,6-pyridinylene;

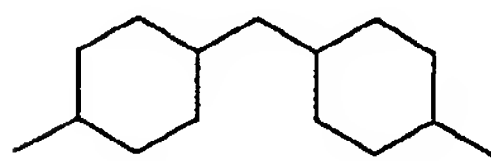
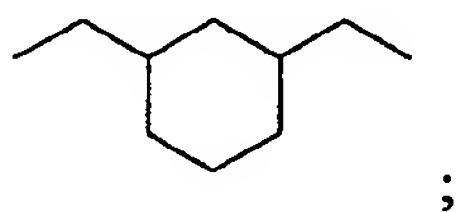
1,2-cyclohexylene;

5

1,3-cyclohexylene;

1,4-cyclohexylene;

trans-1,4-cyclohexylene;



; and

10

trans-5-norbornen-2,3-diyl;

wherein n is 0 - 4; each R is independently selected from the group consisting of C<sub>1-4</sub> alkyl, C<sub>1-4</sub> alkoxy, and halogen; and Q is selected from the group consisting of a bond, -CH<sub>2</sub>-, and -O-;

R<sub>231</sub> is selected from the group consisting of:

15

-hydrogen;

-alkyl;

-alkenyl;

-aryl;

-substituted aryl;

20

-heteroaryl;

-substituted heteroaryl;

-alkyl-X-alkyl;

-alkyl-X-aryl;

-alkyl-X-alkenyl; and

25

-alkyl or alkenyl substituted by one or more substituents selected from the group consisting of:

-OH;

-halogen;

- N(R<sub>631</sub>)<sub>2</sub>;
- C(O)-N(R<sub>631</sub>)<sub>2</sub>;
- C(S)-N(R<sub>631</sub>)<sub>2</sub>;
- S(O)<sub>2</sub>-N(R<sub>631</sub>)<sub>2</sub>;
- 5 -N(R<sub>631</sub>)-C(O)-C<sub>1-10</sub> alkyl;
- N(R<sub>631</sub>)-C(S)-C<sub>1-10</sub> alkyl;
- N(R<sub>631</sub>)-S(O)<sub>2</sub>-C<sub>1-10</sub> alkyl;
- C(O)-C<sub>1-10</sub> alkyl;
- C(O)-O-C<sub>1-10</sub> alkyl;
- 10 -N<sub>3</sub>;
- aryl;
- substituted aryl;
- heteroaryl;
- substituted heteroaryl;
- 15 -heterocyclyl;
- substituted heterocyclyl;
- C(O)-aryl;
- C(O)-(substituted aryl);
- C(O)-heteroaryl; and
- 20 -C(O)-(substituted heteroaryl);

R<sub>331</sub> and R<sub>431</sub> are each independently selected from the group consisting of:

- hydrogen;
- halogen;
- alkyl;
- 25 -alkenyl;
- X-alkyl; and
- N(R<sub>631</sub>)<sub>2</sub>;

or when taken together, R<sub>331</sub> and R<sub>431</sub> form a fused aryl or heteroaryl ring that is unsubstituted or substituted by one or more substituents selected from the group consisting of:

- halogen;
- alkyl;

-alkenyl;  
 -X-alkyl; and  
 -N(R<sub>631</sub>)<sub>2</sub>;

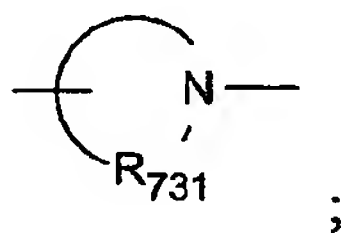
or when taken together, R<sub>331</sub> and R<sub>431</sub> form a fused 5 to 7 membered saturated ring, containing 0 to 2 heteroatoms and unsubstituted or substituted by one or more substituents selected from the group consisting of:

-halogen;  
 -alkyl;  
 -alkenyl;  
 -X-alkyl; and  
 -N(R<sub>631</sub>)<sub>2</sub>;

each R<sub>531</sub> is independently selected from the group consisting of:

hydrogen;  
 C<sub>1-6</sub> alkyl;  
 C<sub>3-7</sub> cycloalkyl; and  
 benzyl; or

when Y is -N(R<sub>531</sub>)C(O)-, -C(O)N(R<sub>531</sub>)-, -N(R<sub>531</sub>)C(O)N(R<sub>531</sub>)-, -N(R<sub>531</sub>)S(O)<sub>2</sub>-, -S(O)<sub>2</sub>N(R<sub>531</sub>)-, -N(R<sub>531</sub>)C(O)O-, or -OC(O)N(R<sub>531</sub>)- and the nitrogen of the N(R<sub>531</sub>) group is bonded to Z, then R<sub>531</sub> can join with Z to form a ring having the structure



each R<sub>631</sub> is independently hydrogen or C<sub>1-10</sub> alkyl;

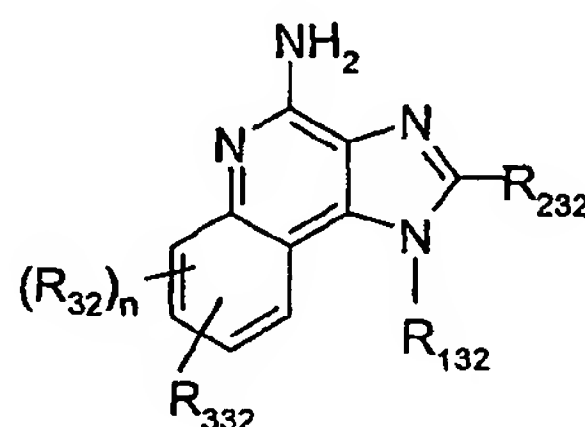
R<sub>731</sub> is C<sub>3-8</sub> alkylene; and

X is -O- or -S-;

with the proviso that if W is -C(O)-, -S(O)<sub>2</sub>-, -OC(O)O-, or -N(R<sub>531</sub>)C(O)N(R<sub>531</sub>)- then each Y is a bond;

and pharmaceutically acceptable salts thereof.

In another embodiment, the IRM compound can be chosen from 6-, 7-, 8-, or 9-position aryl or heteroaryl substituted 1*H*-imidazo[4,5-*c*]quinolin-4-amines of the following Formula (XXXII):



XXXII

wherein:

$R_{32}$  is selected from the group consisting of alkyl, alkoxy, hydroxy, and trifluoromethyl;

$n$  is 0 or 1;

$R_{132}$  and  $R_{232}$  are independently selected from the group consisting of hydrogen and non-interfering substituents;

$R_{332}$  is selected from the group consisting of:

- Z-Ar,
- Z-Ar'-Y- $R_{432}$ ,
- Z-Ar'-X-Y- $R_{432}$ ,
- Z-Ar'- $R_{532}$ , and
- Z-Ar'-X- $R_{532}$ ;

Ar is selected from the group consisting of aryl and heteroaryl both of which can be unsubstituted or can be substituted by one or more substituents independently selected from the group consisting of alkyl, alkenyl, alkoxy, methylenedioxy, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, hydroxyalkyl, mercapto, cyano, carboxy, formyl, aryl, aryloxy, arylalkoxy, heteroaryl, heteroaryloxy, heteroarylalkoxy, heterocyclyl, heterocyclylalkyl, amino, alkylamino, and dialkylamino;

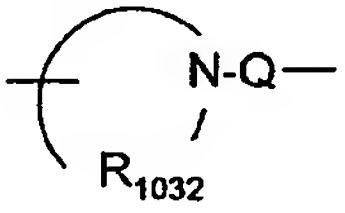
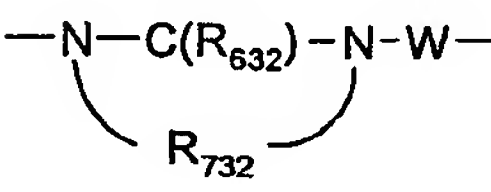
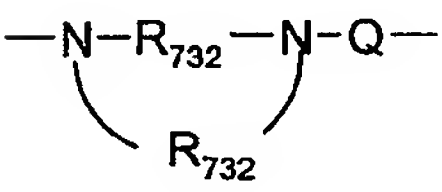
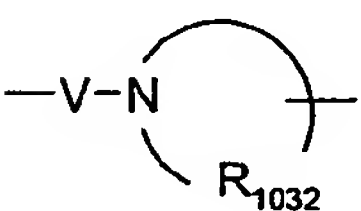
Ar' is selected from the group consisting of arylene and heteroarylene both of which can be unsubstituted or can be substituted by one or more substituents independently selected from the group consisting of alkyl, alkenyl, alkoxy, haloalkyl,

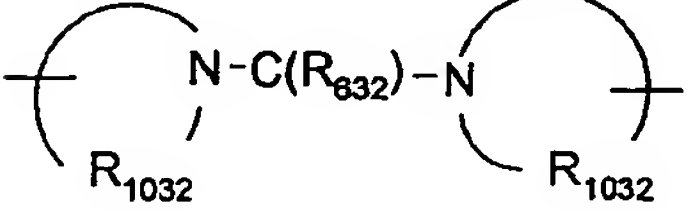
haloalkoxy, halogen, nitro, hydroxy, hydroxyalkyl, mercapto, cyano, carboxy, formyl, aryl, aryloxy, arylalkoxy, heteroaryl, heteroaryloxy, heteroarylalkoxy, heterocyclyl, heterocyclalkyl, amino, alkylamino, and dialkylamino;

X is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated with arylene, heteroarylene, or heterocyclylene, and optionally interrupted by one or more -O- groups;

Y is selected from the group consisting of:

10                   -S(O)<sub>0-2</sub>-,  
                   -S(O)<sub>2</sub>-N(R<sub>832</sub>)-,  
                   -C(R<sub>632</sub>)-,  
                   -C(R<sub>632</sub>)-O-,  
                   -O-C(R<sub>632</sub>)-,  
                   -O-C(O)-O-,  
 15               -N(R<sub>832</sub>)-Q-,  
                   -C(R<sub>632</sub>)-N(R<sub>832</sub>)-,  
                   -O-C(R<sub>632</sub>)-N(R<sub>832</sub>)-,  
                   -C(R<sub>632</sub>)-N(OR<sub>932</sub>)-,

20                   ,  
                   ,  
                   ,  
                   , and

;



and pharmaceutically acceptable salts thereof.

Illustrative non-interfering  $R_{132}$  substituents include:

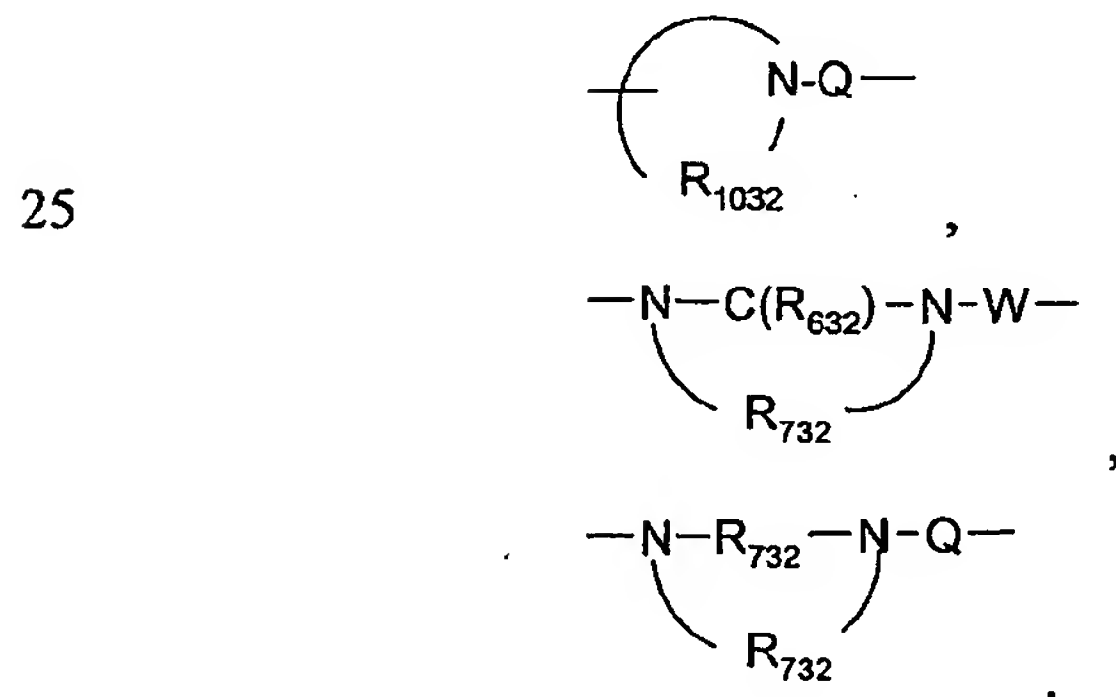
- 5  
 $-R_{432}$ ,  
 $-X-R_{432}$ ,  
 $-X-Y-R_{432}$ ,  
 $-X-Y-X-Y-R_{432}$ , and  
 $-X-R_{532}$ ;

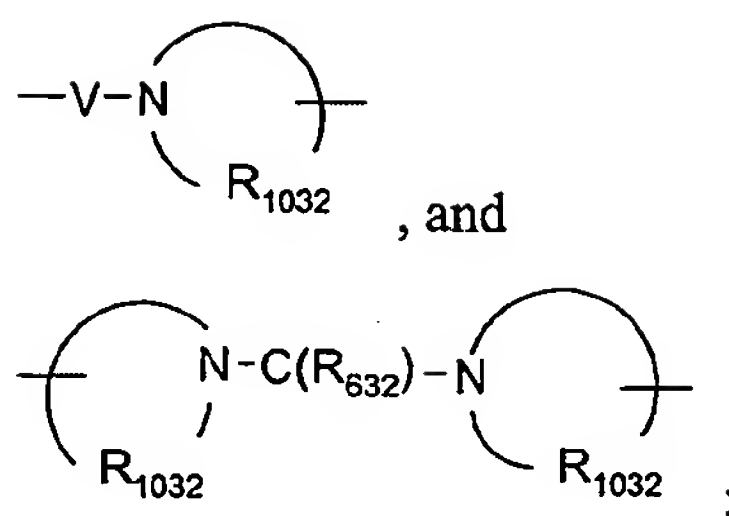
wherein:

10 each X is independently selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated with arylene, heteroarylene, or heterocyclylene, and optionally interrupted by one or more -O-

each Y is independently selected from the group consisting of:

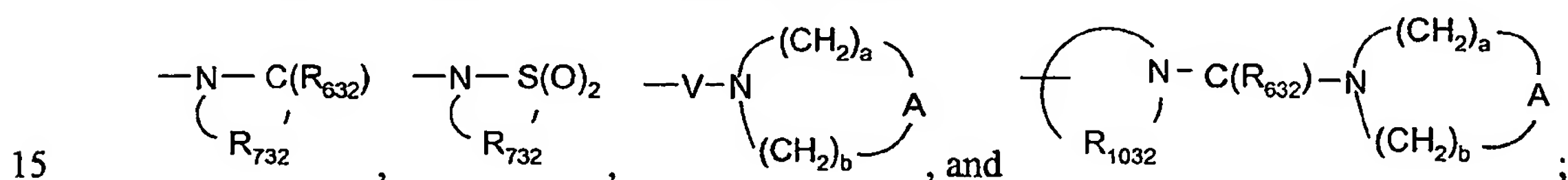
- 15  
 $-S(O)_{0-2}-$ ,  
 $-S(O)_2-N(R_{832})-$ ,  
 $-C(R_{632})-$ ,  
 $-C(R_{632})-O-$ ,  
 $-O-C(R_{632})-$ ,  
20  $-O-C(O)-O-$ ,  
 $-N(R_{832})-Q-$ ,  
 $-C(R_{632})-N(R_{832})-$ ,  
 $-O-C(R_{632})-N(R_{832})-$ ,  
 $-C(R_{632})-N(OR_{932})-$ ,





$R_{432}$  is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

$R_{532}$  is selected from the group consisting of:



each  $R_{632}$  is independently selected from the group consisting of =O and =S;

each  $R_{732}$  is independently  $C_{2-7}$  alkylene;

each  $R_{832}$  is independently selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, and arylalkylenyl;

each  $R_{932}$  is independently selected from the group consisting of hydrogen and alkyl;

each  $R_{1032}$  is independently  $C_{3-8}$  alkylene;

A is selected from the group consisting of -O-, -C(O)-, -S(O)<sub>0-2</sub>-, -CH<sub>2</sub>-, and -N( $R_{432}$ )-;

each Q is independently selected from the group consisting of a bond, -C( $R_{632}$ )-, -C( $R_{632}$ )-C( $R_{632}$ )-, -S(O)<sub>2</sub>-, -C( $R_{632}$ )-N( $R_{832}$ )-W-, -S(O)<sub>2</sub>-N( $R_{832}$ )-, -C( $R_{632}$ )-O-, and -C( $R_{632}$ )-N(OR<sub>932</sub>)-;

each V is independently selected from the group consisting of -C(R<sub>632</sub>)-, -O-C(R<sub>632</sub>)-, -N(R<sub>832</sub>)-C(R<sub>632</sub>)-, and -S(O)<sub>2</sub>-;

each W is independently selected from the group consisting of a bond, -C(O)-, and -S(O)<sub>2</sub>-; and

5 a and b are independently integers from 1 to 6 with the proviso that  $a + b$  is  $\leq 7$ ;

**Illustrative non-interfering R<sub>232</sub> substituents include:**

-R432,

-X-R<sub>432</sub>.

-X-Y-R<sub>432</sub>, and

10 -X-R<sub>532</sub>;

wherein:

X is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated with arylene, heteroarylene, or heterocyclylene, and optionally interrupted by one or more -O- groups;

Y is selected from the group consisting of:

$$-\text{S}(\text{O})_{0-2}-,$$
$$-\text{S}(\text{O})_2-\text{N}(\text{R}_{832})-$$

-C(R<sub>632</sub>)-,

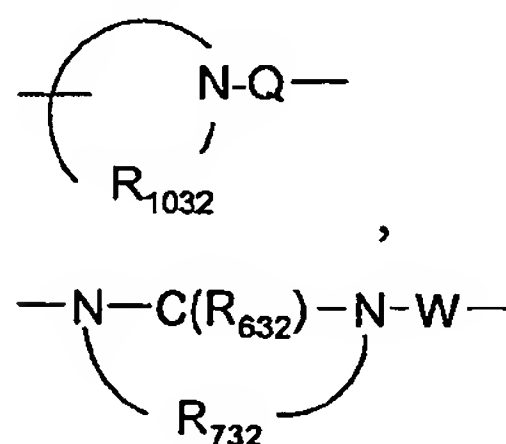
20  $-\text{C}(\text{R}_{632})-\text{O}-$ ,

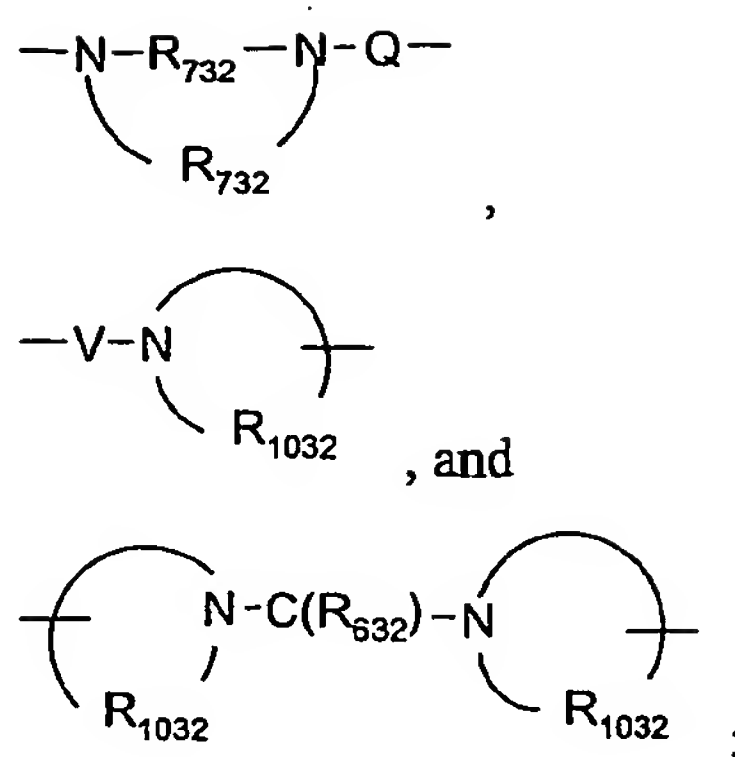
$$-\text{C}(\text{R}_{632})-\text{O}-,$$
$$-\text{O}-\text{C}(\text{R}_{632})-$$
$$-\text{O}-\text{C}(\text{O})-\text{O}-,$$

-N(R<sub>832</sub>)-Q-

$$-\text{C}(\text{R}_{632})-\text{N}(\text{R}_{832})-$$

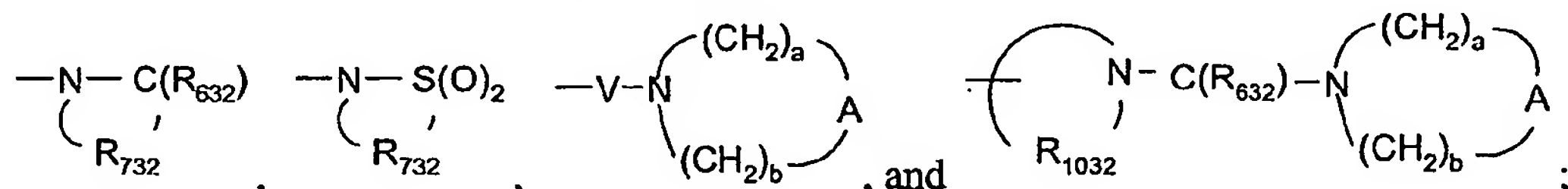
25  $-O-C(R_{632})-N(R_{832})-$ ,

$$-\text{O}-\text{C}(\text{R}_{632})-\text{N}(\text{R}_{832})-$$
$$-\text{C}(\text{R}_{632})-\text{N}(\text{OR}_{932})-$$




$R_{432}$  is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl,  
 5 aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl,  
 heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl,  
 alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl,  
 heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups  
 can be unsubstituted or substituted by one or more substituents independently selected  
 10 from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen,  
 nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy,  
 heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino,  
 (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl,  
 oxo;

15  $R_{532}$  is selected from the group consisting of:



each  $R_{632}$  is independently selected from the group consisting of =O and =S;

each  $R_{732}$  is independently  $C_{2-7}$  alkylene;

20 each  $R_{832}$  is independently selected from the group consisting of hydrogen, alkyl,  
 alkoxyalkylenyl, and arylalkylenyl;

$R_{932}$  is selected from the group consisting of hydrogen and alkyl;

each  $R_{1032}$  is independently  $C_{3-8}$  alkylene;

A is selected from the group consisting of -O-, -C(O)-, -S(O)<sub>0-2</sub>-, -CH<sub>2</sub>-, and -  
 N( $R_{432}$ )-;

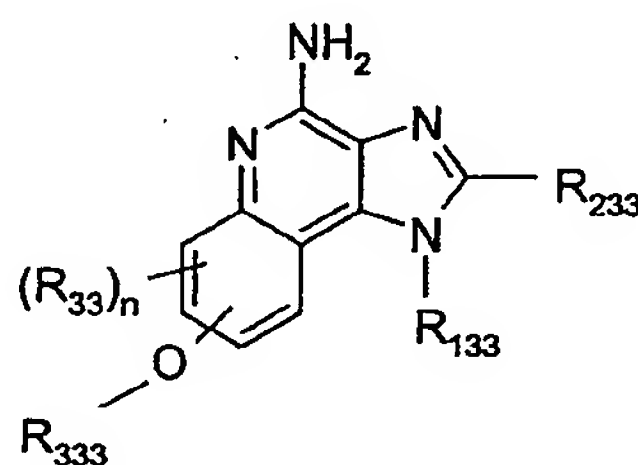
25 Q is selected from the group consisting of a bond, -C( $R_{632}$ )-,

-C(R<sub>632</sub>)-C(R<sub>632</sub>)-, -S(O)<sub>2</sub>-, -C(R<sub>632</sub>)-N(R<sub>832</sub>)-W-, -S(O)<sub>2</sub>-N(R<sub>832</sub>)-, -C(R<sub>632</sub>)-O-, and -C(R<sub>632</sub>)-N(OR<sub>932</sub>)-;

V is selected from the group consisting of -C(R<sub>632</sub>)-, -O-C(R<sub>632</sub>)-, -N(R<sub>832</sub>)-C(R<sub>632</sub>)-, and -S(O)<sub>2</sub>-;

5 W is selected from the group consisting of a bond, -C(O)-, and -S(O)<sub>2</sub>-; and  
a and b are independently integers from 1 to 6 with the proviso that a + b is ≤ 7;

In another embodiment, the IRM compound can be chosen from aryloxy or  
arylalkyleneoxy substituted 1*H*-imidaz[4,5-*c*]quinoline-4-amines of the following  
10 Formula XXXIII:



XXXIII

wherein:

R<sub>333</sub> is selected from the group consisting of:

15 -Z-Ar,  
-Z-Ar'-Y-R<sub>433</sub>,  
-Z-Ar'-X-Y-R<sub>433</sub>,  
-Z-Ar'-R<sub>533</sub>, and  
-Z-Ar'-X-R<sub>533</sub>;

20 Z is selected from the group consisting of a bond, alkylene, alkenylene, and  
alkynylene wherein alkylene, alkenylene, and alkynylene are optionally interrupted with -  
O-;

Ar is selected from the group consisting of aryl and heteroaryl both of which can  
be unsubstituted or can be substituted by one or more substituents independently selected  
25 from the group consisting of alkyl, alkenyl, alkoxy, methylenedioxy, haloalkyl,  
haloalkoxy, halogen, nitro, hydroxy, hydroxyalkyl, mercapto, cyano, carboxy, formyl,  
aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy,  
heterocyclyl, heterocyclylalkylenyl, amino, alkylamino, and dialkylamino;

Ar' is selected from the group consisting of arylene and heteroarylene both of which can be unsubstituted or can be substituted by one or more substituents independently selected from the group consisting of alkyl, alkenyl, alkoxy, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, hydroxyalkyl, mercapto, cyano, carboxy, formyl, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, heterocyclylalkylenyl, amino, alkylamino, and dialkylamino;

R<sub>33</sub> is selected from the group consisting of alkyl, alkoxy, hydroxy, halogen, and trifluoromethyl;

n is 0 or 1;

R<sub>133</sub> is selected from the group consisting of:

-R<sub>433</sub>,  
 -X-R<sub>433</sub>,  
 -X-Y-R<sub>433</sub>,  
 -X-Y-X-Y-R<sub>433</sub>, and  
 -X-R<sub>533</sub>;

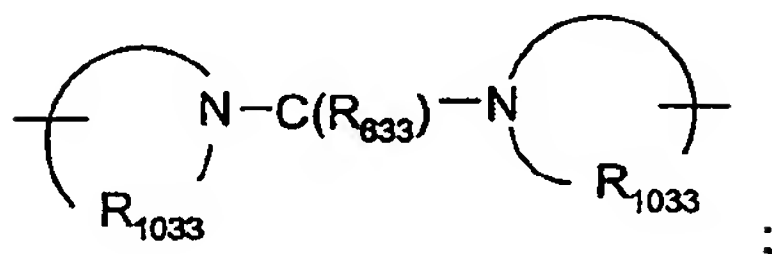
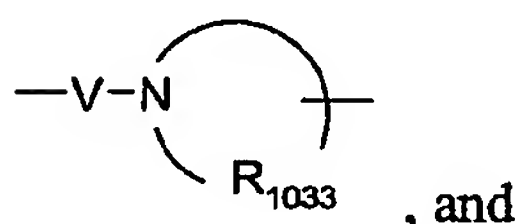
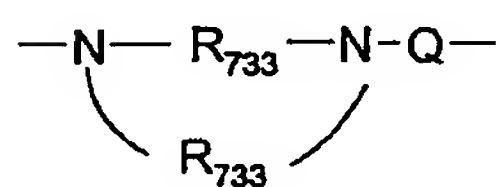
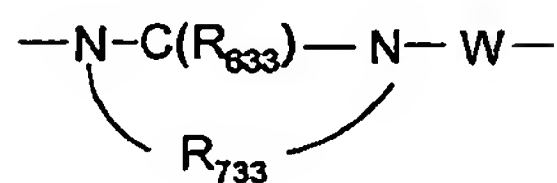
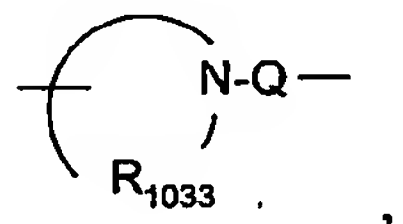
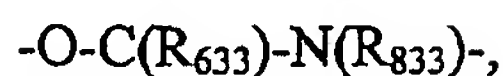
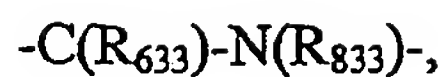
R<sub>233</sub> is selected from the group consisting of:

-R<sub>433</sub>,  
 -X-R<sub>433</sub>,  
 -X-Y-R<sub>433</sub>, and  
 -X-R<sub>533</sub>;

each X is independently selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted by arylene, heteroarylene or heterocyclylene or by one or more -O- groups;

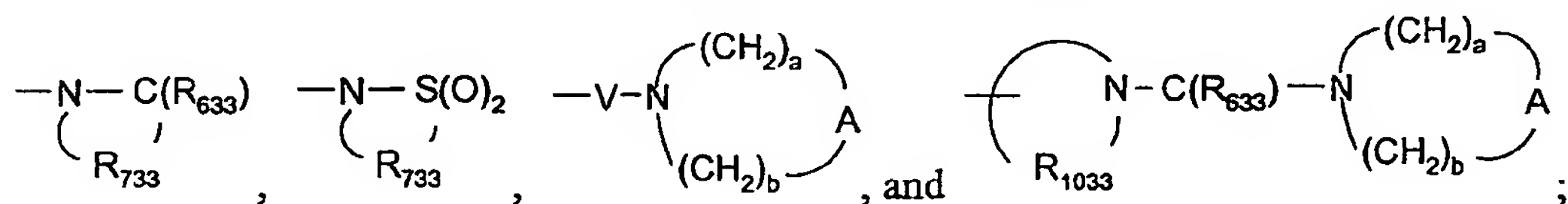
each Y is independently selected from the group consisting of:

-S(O)<sub>0-2</sub>-,  
 -S(O)<sub>2</sub>-N(R<sub>833</sub>)-,  
 -C(R<sub>633</sub>)-,  
 -C(R<sub>633</sub>)-O-,  
 -O-C(R<sub>633</sub>)-,  
 -O-C(O)-O-,  
 -N(R<sub>833</sub>)-Q-,



each  $R_{433}$  is independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

each  $R_{533}$  is independently selected from the group consisting of:



each  $R_{633}$  is independently selected from the group consisting of =O and =S;

each  $R_{733}$  is independently  $C_{2-7}$  alkylene;

each  $R_{833}$  is independently selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, and arylalkylenyl;

each  $R_{933}$  is independently selected from the group consisting of hydrogen and alkyl;

each  $R_{1033}$  is independently  $C_{3-8}$  alkylene;

each A is independently selected from the group consisting of -O-, -C(O)-, -S(O)<sub>0-2</sub>-, -CH<sub>2</sub>-, and -N( $R_{433}$ )-

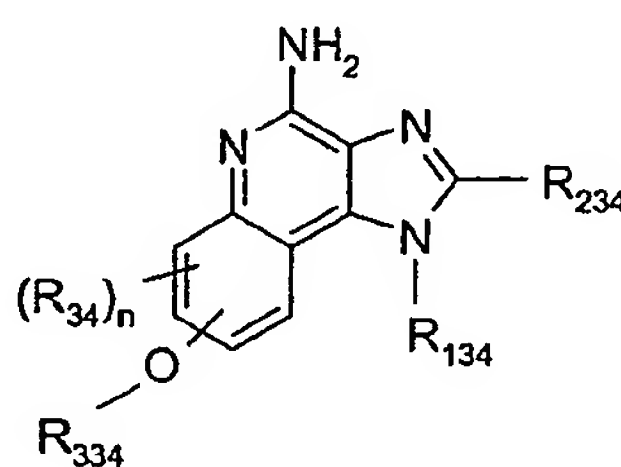
each Q is independently selected from the group consisting of a bond, -C( $R_{633}$ )-, -C( $R_{633}$ )-C( $R_{633}$ )-, -S(O)<sub>2</sub>-, -C( $R_{633}$ )-N( $R_{833}$ )-W-, -S(O)<sub>2</sub>-N( $R_{833}$ )-, -C( $R_{633}$ )-O-, and -C( $R_{633}$ )-N(OR<sub>933</sub>)-

each V is independently selected from the group consisting of -C( $R_{633}$ )-, -O-C( $R_{633}$ )-, -N( $R_{833}$ )-C( $R_{633}$ )-, and -S(O)<sub>2</sub>-;

each W is independently selected from the group consisting of a bond, -C(O)-, and -S(O)<sub>2</sub>-; and

a and b are independently integers from 1 to 6 with the proviso that  $a + b \leq 7$ ; or a pharmaceutically acceptable salt thereof.

In another embodiment, the IRM compound can be chosen from 1*H*-imidaz[4,5-*c*]quinoline-4-amines of the following Formula XXXIV:



XXXIV

wherein:

$R_{334}$  is selected from the group consisting of

-Z-Y- $R_{434}$ ,

-Z-Y-X-Y- $R_{434}$ ,

-Z-R<sub>534</sub>,  
 -Z-Het,  
 -Z-Het'-R<sub>434</sub>, and  
 -Z-Het'-Y-R<sub>434</sub>;

5           Z is selected from the group consisting of alkylene, alkenylene, and alkynylene, wherein alkylene, alkenylene, and alkynylene can be optionally interrupted with one or more -O- groups;

          R is selected from the group consisting of alkyl, alkoxy, hydroxy, halogen, and trifluoromethyl;

10           n is 0 or 1;

          R<sub>1</sub> is selected from the group consisting of

-R<sub>434</sub>,  
 -X-R<sub>434</sub>,  
 -X-Y-R<sub>434</sub>,  
 15           -X-Y-X-Y-R<sub>434</sub>, and  
 -X-R<sub>534</sub>;

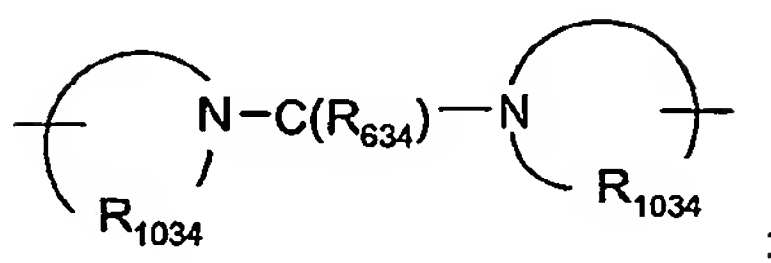
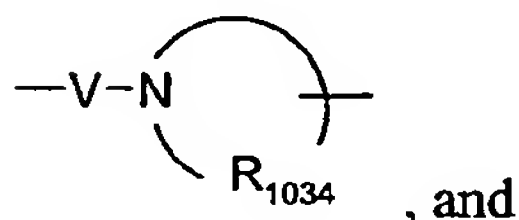
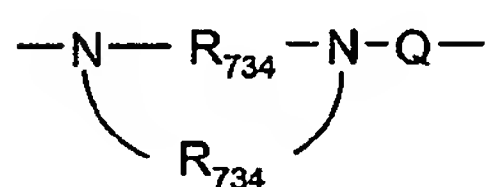
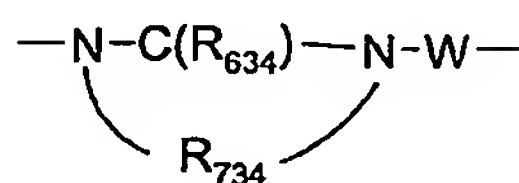
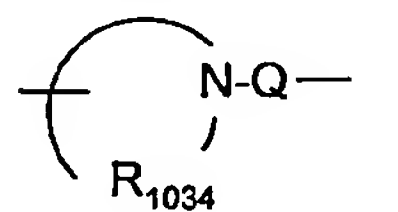
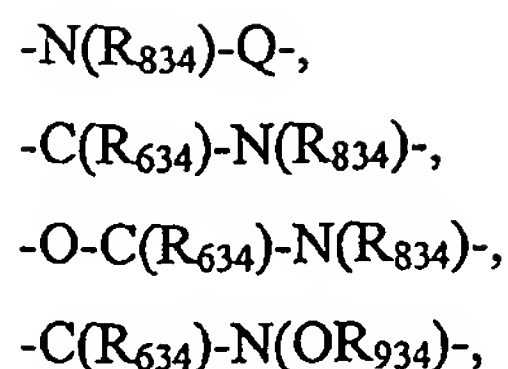
          R<sub>234</sub> is selected from the group consisting of

-R<sub>434</sub>,  
 -X-R<sub>434</sub>,  
 20           -X-Y-R<sub>434</sub>, and  
 -X-R<sub>534</sub>;

          X is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated with arylene, heteroarylene, 25 or heterocyclylene, and optionally interrupted by one or more -O- groups;

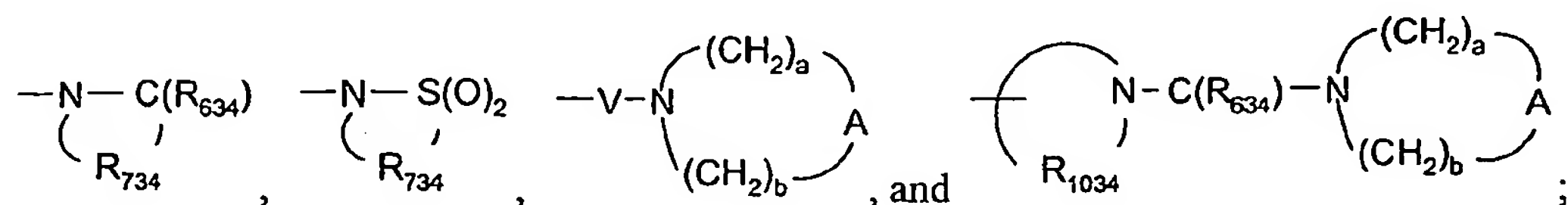
          Y is selected from the group consisting of

-S(O)<sub>0-2</sub>-,  
 -S(O)<sub>2</sub>-N(R<sub>834</sub>)-,  
 -C(R<sub>634</sub>)-,  
 30           -C(R<sub>634</sub>)-O-,  
 -O-C(R<sub>634</sub>)-,  
 -O-C(O)-O-,



10  $R_{434}$  is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups  
15 can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl,  
20 oxo;

$R_{534}$  is selected from the group consisting of



$R_{634}$  is selected from the group consisting of =O and =S;

$R_{734}$  is  $C_{2-7}$  alkylene;

$R_{834}$  is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, and arylalkylenyl;

5  $R_{934}$  is selected from the group consisting of hydrogen and alkyl;

$R_{1034}$  is  $C_{3-8}$  alkylene;

A is selected from the group consisting of -O-, -C(O)-, -S(O)<sub>0-2</sub>-, and -N( $R_{434}$ )-

10 Het is heterocyclyl which can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, hydroxyalkyl, mercapto, cyano, aryloxy, arylalkyleneoxy, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, hydroxyalkyleneoxyalkylenyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and oxo;

15 Het' is heterocyclylene which can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, hydroxyalkyl, mercapto, cyano, aryloxy, arylalkyleneoxy, heteroaryloxy, heteroarylalkyleneoxy, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and oxo;

20 Q is selected from the group consisting of a bond, -C( $R_{634}$ )-, -C( $R_{634}$ )-C( $R_{634}$ )-, -S(O)<sub>2</sub>-, -C( $R_{634}$ )-N( $R_{834}$ )-W-, -S(O)<sub>2</sub>-N( $R_{834}$ )-, -C( $R_{634}$ )-O-, and -C( $R_{634}$ )-N(OR<sub>934</sub>)-

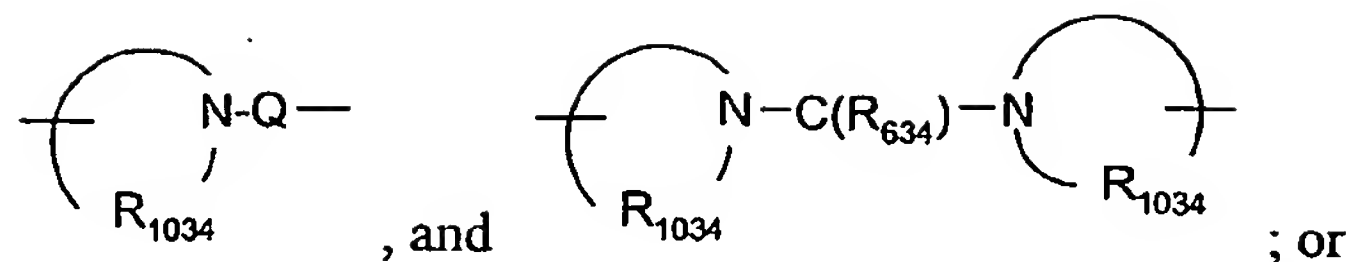
V is selected from the group consisting of -C( $R_{634}$ )-, -O-C( $R_{634}$ )-, -N( $R_{834}$ )-C( $R_{634}$ )-, and -S(O)<sub>2</sub>-;

25 W is selected from the group consisting of a bond, -C(O)-, and -S(O)<sub>2</sub>-; and a and b are independently integers from 1 to 6 with the proviso that  $a + b \leq 7$ ; with the proviso that Z can also be a bond when:

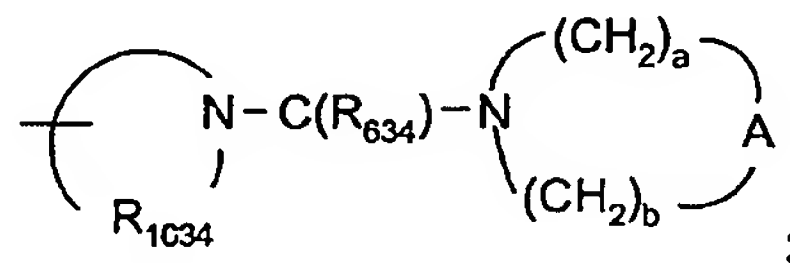
$R_{334}$  is -Z-Het, -Z-Het'- $R_{434}$ , or -Z-Het'-Y- $R_{434}$ ; or

$R_{334}$  is -Z-Y- $R_{434}$  or -Z-Y-X-Y- $R_{434}$ , and Y is selected from

30 -S(O)<sub>0-2</sub>-, -S(O)<sub>2</sub>-N( $R_{834}$ )-, -C( $R_{634}$ )-, -C( $R_{634}$ )-O-, -C( $R_{634}$ )-N( $R_{834}$ )-,



$\text{R}_{334}$  is  $\text{---Z---R}_{534}$  and  $\text{R}_{534}$  is



or a pharmaceutically acceptable salt thereof.

5

Herein, "non-interfering" means that the ability of the compound or salt to modulate (e.g., induce or inhibit) the biosynthesis of one or more cytokines is not destroyed by the non-interfering substituent.

As used herein, the terms "alkyl," "alkenyl," "alkynyl" and the prefix "alk-" are inclusive of both straight chain and branched chain groups and of cyclic groups, i.e. cycloalkyl and cycloalkenyl. Unless otherwise specified, these groups contain from 1 to 20 carbon atoms, with alkenyl and alkynyl groups containing from 2 to 20 carbon atoms. In some embodiments, these groups have a total of up to 10 carbon atoms, up to 8 carbon atoms, up to 6 carbon atoms, or up to 4 carbon atoms. Cyclic groups can be monocyclic or polycyclic and preferably have from 3 to 10 ring carbon atoms. Exemplary cyclic groups include cyclopropyl, cyclopropylmethyl, cyclopentyl, cyclohexyl, adamantyl, and substituted and unsubstituted bornyl, norbornyl, and norbornenyl.

Unless otherwise specified, "alkylene," "alkenylene," and "alkynylene" are the divalent forms of the "alkyl," "alkenyl," and "alkynyl" groups defined above. For example, an arylalkenyl group comprises an alkylene moiety to which an aryl group is attached.

The term "haloalkyl" is inclusive of groups that are substituted by one or more halogen atoms, including perfluorinated groups. This is also true of other groups that include the prefix "halo-." Examples of suitable haloalkyl groups are chloromethyl, trifluoromethyl, and the like.

The term "aryl" as used herein includes carbocyclic aromatic rings or ring systems. Examples of aryl groups include phenyl, naphthyl, biphenyl, fluorenyl, and indenyl.

The term "hetero atom" refers to the atoms O, S, or N.

The term "heteroaryl" includes aromatic rings or ring systems that contain at least one ring hetero atom. Suitable heteroaryl groups include furyl, thienyl, pyridyl, quinoliny, isoquinoliny, indolyl, isoindolyl, triazolyl, pyrrolyl, tetrazolyl, imidazolyl, pyrazolyl, oxazolyl, thiazolyl, benzofuranyl, benzothiophenyl, carbazolyl, benzoxazolyl, pyrimidinyl, benzimidazolyl, quinoxaliny, benzothiazolyl, naphthyridinyl, isoxazolyl, isothiazolyl, purinyl, quinazolinyl, pyrazinyl, 1-oxidopyridyl, pyridazinyl, triazinyl, tetrazinyl, oxadiazolyl, thiadiazolyl, and so on.

The term "heterocyclyl" includes non-aromatic rings or ring systems that contain at least one ring hetero atom and includes all of the fully saturated and partially unsaturated derivatives of the above mentioned heteroaryl groups. Exemplary heterocyclic groups include pyrrolidinyl, tetrahydrofuranyl, morpholinyl, thiomorpholinyl, piperidinyl, piperazinyl, thiazolidinyl, imidazolidinyl, isothiazolidinyl, tetrahydropyranyl, quinuclidinyl, homopiperidinyl, homopiperazinyl, and the like.

The terms "arylene," "heteroarylene," and "heterocyclylene" are the divalent forms of the "aryl," "heteroaryl," and "heterocyclyl" groups defined above. Likewise, "arylenyl," "heteroarylenyl," and "heterocyclenyl" are the divalent forms of the "aryl," "heteroaryl," and "heterocyclyl" groups defined above. For example, an alkylarylenyl group comprises an arylene moiety to which an alkyl group is attached.

Unless otherwise specified, the aryl, heteroaryl, and heterocyclyl groups of Formulas IX - XXXIV can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, methylenedioxy, ethylenedioxy, alkylthio, haloalkyl, haloalkoxy, haloalkylthio, halogen, nitro, hydroxy, mercapto, cyano, carboxy, formyl, aryl, aryloxy, arylthio, arylalkoxy, arylalkylthio, heteroaryl, heteroaryloxy, heteroarylthio, heteroarylalkoxy, heteroarylalkylthio, amino, alkylamino, dialkylamino, heterocyclyl, heterocycloalkyl, alkylcarbonyl, alkenylcarbonyl, alkoxycarbonyl, haloalkylcarbonyl, haloalkoxycarbonyl, alkylthiocarbonyl, arylcarbonyl, heteroarylcarbonyl, heterocyclylcarbonyl, aryloxycarbonyl, heteroaryloxycarbonyl, arylthiocarbonyl, heteroarylthiocarbonyl, alkanoyloxy, alkanoylthio, alkanoylamino, aroyloxy, aroylthio, aroylamino, alkylaminosulfonyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, aryldiazinyl, alkylsulfonylamino, arylsulfonylamino, arylalkylsulfonylamino, alkylcarbonylamino, alkenylcarbonylamino, arylcarbonylamino, arylalkylcarbonylamino, heteroarylcarbonylamino, heteroarylalkylcarbonylamino,

alkylsulfonylamino, alkenylsulfonylamino, arylsulfonylamino, arylalkylsulfonylamino, heteroarylsulfonylamino, heteroarylalkylsulfonylamino, alkylaminocarbonyl, dialkylaminocarbonyl, arylaminocarbonyl, arylalkylaminocarbonyl, alkenylaminocarbonyl, heteroarylaminocarbonyl, heteroarylalkylaminocarbonyl, alkylaminocarbonylamino, alkenylaminocarbonylamino, arylaminocarbonylamino, arylalkylaminocarbonylamino, heteroarylaminocarbonylamino, heteroarylalkylaminocarbonylamino and, in the case of heterocyclyl, oxo. If any other groups are identified as being "substituted" or "optionally substituted," then those groups can also be substituted by one or more of the above enumerated substituents.

10       The IRM compounds and salts thereof described herein include any of their pharmaceutically acceptable forms, such as isomers (e.g., diastereomers and enantiomers), solvates, polymorphs, and the like. In particular, if a compound is optically active, the invention specifically includes the use of each of the compound's enantiomers as well as racemic mixtures of the enantiomers.

15       In some applications, for example, the preferred IRM compound is other than imiquimod or S-28463 (i.e., resiquimod: 4-Amino- $\alpha,\alpha$ -dimethyl-1H-imidazo[4,5-c]quinoline-1-ethanol).

Examples of particular IRM compounds include 2-propyl[1,3]thiazolo[4,5-c]quinolin-4-amine, which is considered predominantly a TLR8 agonist (and not a substantial TLR7 agonist), 4-amino- $\alpha,\alpha$ -dimethyl-1H-imidazo[4,5-c]quinoline-1-ethanol, which is considered predominantly a TLR7 agonist (and not a substantial TLR8 agonist), and 4-amino-2-(ethoxymethyl)- $\alpha,\alpha$ -dimethyl-6,7,8,9-tetrahydro-1H-imidazo[4,5-c]quinoline-1-ethanol, which is a TLR7 and TLR8 agonist. In addition to its TLR7 activity (and low TLR8 activity), 4-amino- $\alpha,\alpha$ -dimethyl-1H-imidazo[4,5-c]quinoline-1-ethanol has beneficial characteristics, including that it has a much lower CNS effect when delivered systemically compared to imiquimod. Other examples of specific IRM compounds include, e.g., N-[4-(4-amino-2-butyl-1H-imidazo[4,5-c][1,5]naphthyridin-1-yl)butyl]-N'-cyclohexylurea, 2-methyl-1-(2-methylpropyl)-1H-imidazo[4,5-c][1,5]naphthyridin-4-amine, 1-(2-methylpropyl)-1H-imidazo[4,5-c][1,5]naphthyridin-4-amine, N-{2-[4-amino-2-(ethoxymethyl)-1H-imidazo[4,5-c]quinolin-1-yl]-1,1-dimethylethyl}methanesulfonamide, N-[4-(4-amino-2-ethyl-1H-imidazo[4,5-c]quinolin-1-yl)butyl]methanesulfonamide, 2-methyl-1-[5-(methylsulfonyl)pentyl]-1H-imidazo[4,5-

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c]quinolin-4-amine, N-[4-(4-amino-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butyl]methanesulfonamide, 2-butyl-1-[3-(methylsulfonyl)propyl]-1*H*-imidazo[4,5-*c*]quinoline-4-amine, 2-butyl-1-{2-[(1-methylethyl)sulfonyl]ethyl}-1*H*-imidazo[4,5-*c*]quinolin-4-amine, N-{2-[4-amino-2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]-1,1-dimethylethyl}-*N'*-cyclohexylurea, N-{2-[4-amino-2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]-1,1-dimethylethyl}cyclohexanecarboxamide, N-{2-[4-amino-2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]ethyl}-*N'*-isopropylurea. Resiquimod, 4-amino-2-ethoxymethyl- $\alpha,\alpha$ -dimethyl-1*H*-imidazo[4,5-*c*]quinoline-1-ethanol, may also be used in certain situations where a combination TLR 7 and TLR 8 agonist is desired.

### *Exemplary Applications*

Soluble IRM-polymer complexes can be used in a wide variety of applications, such as in the treatment of a wide variety of conditions. For example, IRMs such as imiquimod - a small molecule, imidazoquinoline IRM, marketed as ALDARA (3M Pharmaceuticals, St. Paul, MN) - have been shown to be useful for the therapeutic treatment of warts, as well as certain cancerous or pre-cancerous lesions (See, e.g., Geisse *et al.*, *J. Am. Acad. Dermatol.*, 47(3): 390-398 (2002); Shumack *et al.*, *Arch. Dermatol.*, 138: 1163-1171 (2002); U.S. Pat. No. 5,238,944 and International Publication No. WO 03/045391.

Conditions that may be treated by administering a soluble IRM-polymer complex of the present invention include, but are not limited to:

(a) viral diseases such as, for example, diseases resulting from infection by an adenovirus, a herpesvirus (e.g., HSV-I, HSV-II, CMV, or VZV), a poxvirus (e.g., an orthopoxvirus such as variola or vaccinia, or molluscum contagiosum), a picornavirus (e.g., rhinovirus or enterovirus), an orthomyxovirus (e.g., influenzavirus), a paramyxovirus (e.g., parainfluenzavirus, mumps virus, measles virus, and respiratory syncytial virus (RSV)), a coronavirus (e.g., SARS), a papovavirus (e.g., papillomaviruses, such as those that cause genital warts, common warts, or plantar warts), a hepadnavirus (e.g., hepatitis B virus), a flavivirus (e.g., hepatitis C virus or Dengue virus), or a retrovirus (e.g., a lentivirus such as HIV);

(b) bacterial diseases such as, for example, diseases resulting from infection by bacteria of, for example, the genus *Escherichia*, *Enterobacter*, *Salmonella*, *Staphylococcus*,

Shigella, Listeria, Aerobacter, Helicobacter, Klebsiella, Proteus, Pseudomonas, Streptococcus, Chlamydia, Mycoplasma, Pneumococcus, Neisseria, Clostridium, Bacillus, Corynebacterium, Mycobacterium, Campylobacter, Vibrio, Serratia, Providencia, Chromobacterium, Brucella, Yersinia, Haemophilus, or Bordetella;

5 (c) other infectious diseases, such chlamydia, fungal diseases including but not limited to candidiasis, aspergillosis, histoplasmosis, cryptococcal meningitis, or parasitic diseases including but not limited to malaria, pneumocystis carinii pneumonia, leishmaniasis, cryptosporidiosis, toxoplasmosis, and trypanosome infection; and

10 (d) neoplastic diseases, such as intraepithelial neoplasias, cervical dysplasia, actinic keratosis, basal cell carcinoma, squamous cell carcinoma, renal cell carcinoma, Kaposi's sarcoma, melanoma, renal cell carcinoma, leukemias including but not limited to myelogenous leukemia, chronic lymphocytic leukemia, multiple myeloma, non-Hodgkin's lymphoma, cutaneous T-cell lymphoma, B-cell lymphoma, and hairy cell leukemia, and other cancers;

15 (e)  $T_H2$ -mediated, atopic diseases, such as atopic dermatitis or eczema, eosinophilia, asthma, allergy, allergic rhinitis, and Ommen's syndrome;

(f) certain autoimmune diseases such as systemic lupus erythematosus, essential thrombocythaemia, multiple sclerosis, discoid lupus, alopecia areata; and

20 (g) diseases associated with wound repair such as, for example, inhibition of keloid formation and other types of scarring (e.g., enhancing wound healing, including chronic wounds).

Additionally, a soluble IRM-polymer complex of the present invention may be useful as a vaccine adjuvant for use in conjunction with any material that raises either humoral and/or cell mediated immune response, such as, for example, live viral, bacterial, 25 or parasitic immunogens; inactivated viral, tumor-derived, protozoal, organism-derived, fungal, or bacterial immunogens, toxoids, toxins; self-antigens; polysaccharides; proteins; glycoproteins; peptides; cellular vaccines; DNA vaccines; autologous vaccines; recombinant proteins; glycoproteins; peptides; and the like, for use in connection with, for example, BCG, cholera, plague, typhoid, hepatitis A, hepatitis B, hepatitis C, influenza A, 30 influenza B, parainfluenza, polio, rabies, measles, mumps, rubella, yellow fever, tetanus, diphtheria, hemophilus influenza b, tuberculosis, meningococcal and pneumococcal vaccines, adenovirus, HIV, chicken pox, cytomegalovirus, dengue, feline leukemia, fowl

plague, HSV-1 and HSV-2, hog cholera, Japanese encephalitis, respiratory syncytial virus, rotavirus, papilloma virus, yellow fever, and Alzheimer's Disease.

Certain soluble IRM-polymer complexes of the present invention may be particularly helpful in individuals having compromised immune function. For example, 5 certain complexes may be used for treating the opportunistic infections and tumors that occur after suppression of cell mediated immunity in, for example, transplant patients, cancer patients and HIV patients.

The soluble IRM-polymer complexes of the invention may be particularly beneficial for targeting to solid tumors and cancerous organs or tissue regions. If the 10 residence time of the IRM is extended within the cancerous tissue, it is believed that the body's immune response to the cancer can be enhanced and directly targeted to relevant tumor antigens. This not only may help reduce or eliminate cancer at the targeted site of IRM preparation delivery, but, by sensitizing the immune system to the cancer, may help the immune system attack the cancer in other locations throughout the body. This 15 approach to treatment may be used alone or in conjunction with other treatments for the cancer, such as therapeutic cancer vaccination, antibody-based therapies such as Rituxan and Herceptin, and other chemotherapies.

Examples of cancers that may be particularly suitable for targeting of a soluble IRM-polymer complex to a localized tissue region include, but are not limited to, breast 20 cancer, lung cancer, stomach cancer, head and neck cancer, colorectal cancer, renal cell carcinoma, pancreatic cancer, basal cell carcinoma, cervical cancer, melanoma, prostate cancer, ovarian cancer, and bladder cancer.

The methods, materials, and articles of the present invention may be applicable for any suitable subject. Suitable subjects include, but are not limited to, animals such as, but 25 not limited to, humans, non-human primates, rodents, dogs, cats, horses, pigs, sheep, goats, cows, or birds. IRMs may also be particularly helpful in individuals having compromised immune functioning, such as those with HIV AIDS, transplant patients, and cancer patients.

An amount of an IRM-polymer complex effective for a given therapeutic or 30 prophylactic application is an amount sufficient to achieve the intended therapeutic or prophylactic application. The precise amount of IRM-polymer complex used will vary according to factors known in the art including, but not limited to, the physical and

chemical nature of the IRM compound, the physical and chemical matter of the polymer, the nature of the composition, the intended dosing regimen, the state of the subject's immune system (e.g., suppressed, compromised, stimulated), the method of administering the IRM-polymer complex, and the species to which the IRM-polymer complex is being administered. Accordingly it is not practical to set forth generally the amount that constitutes an amount of IRM and IRM-polymer complex effective for all possible applications. Those of ordinary skill in the art, however, can readily determine an appropriate amount with due consideration of such factors.

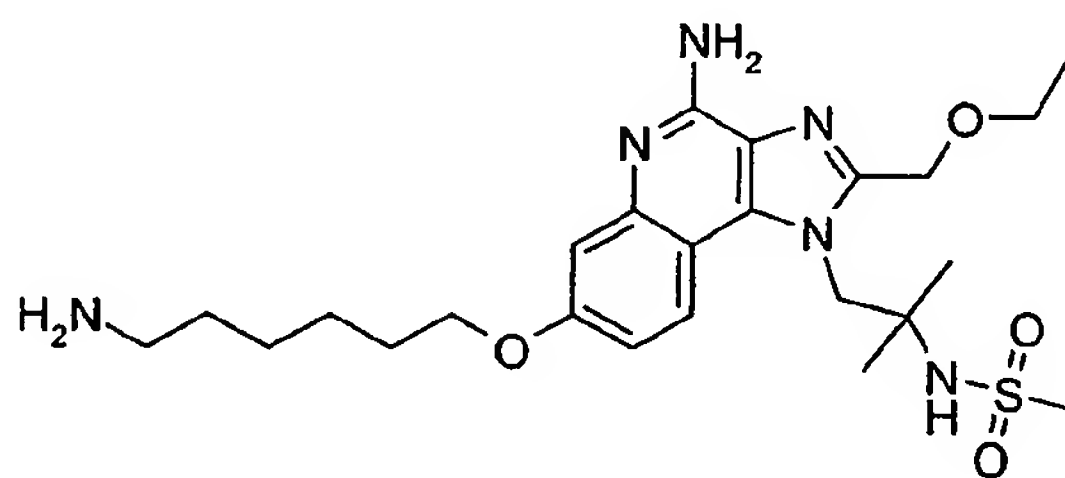
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## EXAMPLES

The following examples are presented merely to further illustrate features, advantages, and other details of the invention. It is to be expressly understood, however, that while the examples serve this purpose, the particular materials and amounts used as well as other conditions and details are not to be construed in a matter that would unduly limit the scope of this invention.

15

Preparation of *N*-{2-[4-amino-7-(6-aminohexyloxy)-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl]-1,1-dimethylethyl}methanesulfonamide



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### Part A

A mixture of triethyl orthoformate (92 milliliters (mL), 0.55 mole (mol)) and 2,2-dimethyl-[1,3]-dioxane-4,6-dione (75.3 g, 0.522 mol) (Meldrum's acid) was heated at 55°C for 90 minutes and then cooled to 45°C. A solution of 3-benzyloxyaniline (100.2 g, 0.5029 mol) in methanol (200 mL) was slowly added to the reaction over a period of 45 minutes while maintaining the reaction temperature below 50°C. The reaction was then heated at 45°C for one hour, allowed to cool to room temperature, and stirred overnight. The reaction mixture was cooled to 1°C, and the product was isolated by filtration and

25

washed with cold ethanol (~400 mL) until the filtrate was colorless. 5-[[[3-benzyloxy)phenylimino]methyl]-2,2-dimethyl-[1,3]-dioxane-4,6-dione (170.65 g) was isolated as a tan, powdery solid.

5      Part B

A mixture of 5-[[[3-benzyloxy)phenylimino]methyl]-2,2-dimethyl-[1,3]-dioxane-4,6-dione (170.65 g, 0.483 mol) and DOWTHERM A (800 mL) was heated to 100°C and then slowly added to a flask containing DOWTHERM A (1.3 L, heated at 210°C) over a period of 40 minutes. During the addition, the reaction temperature was not allowed to  
10      fall below 207°C. Following the addition, the reaction was stirred at 210°C for one hour, and then allowed to cool to ambient temperature. A precipitate formed, which was isolated by filtration, washed with diethyl ether (1.7 L) and acetone (0.5 liter (L)), and dried in an oven to provide 76.5 grams (g) of 7-benzyloxyquinolin-4-ol as a tan powder.

15      Part C

A mixture of 7-benzyloxyquinolin-4-ol (71.47 g, 0.2844 mol) and propionic acid (700 mL) was heated to 125°C with vigorous stirring. Nitric acid (23.11 mL of 16 molar (M)) was slowly added over a period of 30 minutes while maintaining the reaction temperature between 121°C and 125°C. After the addition, the reaction was stirred at  
20      125°C for 1 hour then allowed to cool to ambient temperature. The resulting solid was isolated by filtration, washed with water, and dried in an oven for 1.5 days to provide 69.13 g of 7-benzyloxy-3-nitroquinolin-4-ol as a grayish powder.

Part D

25      *N,N*-Dimethylformamide (100 mL) (DMF) was cooled to 0°C, and phosphorous oxychloride (27.5 mL, 0.295 mol) was added dropwise. The resulting solution was stirred for 25 minutes and then added dropwise to a mixture of 7-benzyloxy-3-nitroquinolin-4-ol (72.87 g, 0.2459 mol) in DMF (400 mL). Following the addition, the reaction was heated at 100°C for 5 minutes, cooled to ambient temperature, and poured into ice water with  
30      stirring. A tan precipitate formed, which was isolated by filtration and dissolved in dichloromethane. The resulting solution was dried over magnesium sulfate, filtered, and

concentrated under reduced pressure to yield 72.9 g of 7-benzyloxy-4-chloro-3-nitroquinoline as a light brown solid.

#### Part E

5           Triethylamine (12.8 mL, 92.0 millimole (mmol)) and 1,2-diamino-2-methylpropane (5.29 mL, 50.6 mmol) were added sequentially to a solution of 7-benzyloxy-4-chloro-3-nitroquinoline (14.5 g, 46.0 mmol) in dichloromethane (400 mL). The reaction mixture was stirred overnight and then concentrated under reduced pressure. The residue was partitioned between water (200 mL) and dichloromethane (300 mL). The  
10           organic layer was washed with brine, dried over sodium sulfate, and then concentrated under reduced pressure to provide crude product as a brown solid. The crude product was passed through a layer of silica gel (eluting sequentially with chloroform and 96:4 chloroform:methanol) to provide 12.4 g of (2-amino-2-methylpropyl)(7-benzyloxy-3-nitroquinolin-4-yl)amine as a yellow solid.

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#### Part F

          Under a nitrogen atmosphere, a solution of (2-amino-2-methylpropyl)(7-benzyloxy-3-nitroquinolin-4-yl)amine (12.4 g, 33.9 mmol) in dichloromethane (400 mL) was cooled to 0°C. Triethylamine (9.43 mL, 67.8 mmol) and methanesulfonic anhydride  
20           (5.90 g, 33.9 mmol) were sequentially added, and the reaction was stirred at ambient temperature for two hours. An analysis by HPLC indicated that the reaction was incomplete, and additional methanesulfonic anhydride (1.4 g, 8.0 mmol) was added. The reaction was stirred for an additional 90 minutes, and additional methanesulfonic anhydride (0.7 g, 4 mmol) was added. The reaction was stirred for an additional three  
25           hours, and saturated aqueous sodium bicarbonate (200 mL) was added. A precipitate began to form in the organic layer, which was separated and concentrated under reduced pressure to provide a yellow solid. The solid was triturated with water (200 mL) with heating, isolated by filtration, washed with water (3 x 100 mL) and diethyl ether (3 x 50 mL), and dried overnight under vacuum to provide 14.8 g of *N*-[1,1-dimethyl-2-(3-nitro-7-benzyloxyquinolin-4-ylamino)ethyl]methanesulfonamide as a yellow powder.  
30

## Part G

*N*-[1,1-Dimethyl-2-(3-nitro-7-benzyloxyquinolin-4-ylamino)ethyl]methanesulfonamide (14.8 g, 33.3 mmol) was mixed with acetonitrile (300 mL) and added to a Parr flask; 5% platinum on carbon (2 g) was added. The reaction was flushed with nitrogen and placed under hydrogen pressure (40 pounds per square inch (psi),  $2.8 \times 10^5$  Pascals (Pa)) for 5.5 hours with the hydrogen replaced after two hours. An analysis by TLC indicated the presence of starting material. Additional acetonitrile (200 mL) and 5% platinum on carbon (2 g) were added, and the reaction was placed under hydrogen pressure overnight. The reaction mixture was filtered through a layer of CELITE filter aid, and the filter cake was washed with acetonitrile. The filtrate was concentrated under reduced pressure. Toluene and dichloromethane were added and removed under reduced pressure twice to yield 12.6 g of *N*-[2-(3-amino-7-benzyloxyquinolin-4-ylamino)-1,1-dimethylethyl]methanesulfonamide as a solid.

## Part H

Under a nitrogen atmosphere, a solution of *N*-[2-(3-amino-7-benzyloxyquinolin-4-ylamino)-1,1-dimethylethyl]methanesulfonamide (12.6 g, 30.4 mmol) in dichloromethane (300 mL) was cooled to  $\sim 0^\circ\text{C}$ ; triethylamine (4.23 mL, 30.4 mmol) was added. Ethoxy acetyl chloride (3.33 mL, 30.4 mmol) was added dropwise, and the reaction was stirred at ambient temperature for 1.5 hours. The volatiles were removed under reduced pressure, and the residue was dissolved in ethanol (300 mL). Triethylamine (13 mL) was added, and the reaction was heated at reflux overnight and allowed to cool to ambient temperature. The volatiles were removed under reduced pressure. The residue was dissolved in dichloromethane (300 mL), and the resulting solution was washed with water (2 x 100 mL) and brine, dried over sodium sulfate, filtered, and concentrated under reduced pressure to provide a brown oil. The oil was purified by column chromatography on silica gel (eluting with 97.5:2.5 chloroform:methanol) to provide 12.4 g of *N*-[2-(7-benzyloxy-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-1,1-dimethylethyl]methanesulfonamide as a beige solid.

## Part I

A solution of *N*-[2-(7-benzyloxy-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-1,1-dimethylethyl]methanesulfonamide (9.38 g, 19.5 mmol) in ethanol (150 mL) was added to a Parr vessel containing 10% palladium on carbon (0.83 g). The reaction was placed under hydrogen pressure (50 psi,  $3.4 \times 10^5$  Pa) over two nights. Starting material  
5 remained as evidenced by a TLC analysis, and additional 10% palladium on carbon (1.02 g) was added. The reaction was continued for an additional eight hours. The reaction mixture was filtered through a layer of CELITE filter aid, and the filter cake was washed with ethanol and methanol. The filtrate was concentrated under reduced pressure, and the residue was dissolved in toluene and concentrated under reduced pressure several times to  
10 yield a yellow powder, which was dried under high vacuum to provide 7.37 g of *N*-[2-(2-ethoxymethyl-7-hydroxy-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-1,1-dimethylethyl]methanesulfonamide as a yellow solid.

#### Part J

15 Under a nitrogen atmosphere, cesium carbonate (9.18 g, 28.2 mmol) was added in a single portion to a solution of *N*-[2-(2-ethoxymethyl-7-hydroxy-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-1,1-dimethylethyl]methanesulfonamide (7.37 g, 18.8 mmol) in DMF. A solution of *tert*-butyl 6-iodohexylcarbamate (6.75 g, 20.6 mmol) in DMF (approximately 100 mL) was added. The reaction mixture was heated overnight at 65°C and then  
20 concentrated under reduced pressure to provide an orange oil. The oil was partitioned between water (300 mL) and dichloromethane (300 mL). The organic layer was washed sequentially with water (x 2) and brine, dried over sodium sulfate, filtered, and then concentrated under reduced pressure. The residue was dissolved in dichloromethane (100 mL), washed sequentially with water (x 10) and brine, dried over sodium sulfate, filtered,  
25 and then concentrated under reduced pressure to provide 10.85 g of crude product as a yellow foam. The crude product was purified by column chromatography on silica gel (eluting sequentially with 95:5 and 92.5:7.5 dichloromethane:methanol) to provide 8.5 g of *tert*-butyl {6-[2-ethoxymethyl-1-(2-methanesulfonylamino-2-methylpropyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yloxy]hexyl}carbamate as a white solid.

30

#### Part K

3-Chloroperoxybenzoic acid (4.23 g of 60%, 14.4 mmol) was added in a single portion to a solution of *tert*-butyl {6-[2-ethoxymethyl-1-(2-methanesulfonylamino-2-methylpropyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yloxy]hexyl} carbamate (8.5 g, 14.4 mmol) in chloroform (200 mL). The reaction mixture was stirred for several hours and then washed sequentially with 1% sodium carbonate (x 2) and brine. The organic layer was dried over sodium sulfate, filtered, and then concentrated under reduced pressure to provide 9.20 g of *tert*-butyl {6-[2-ethoxymethyl-1-(2-methanesulfonylamino-2-methylpropyl)-5-oxido-1*H*-imidazo[4,5-*c*]quinolin-1-yloxy]hexyl} carbamate as a orange solid.

10 Part L

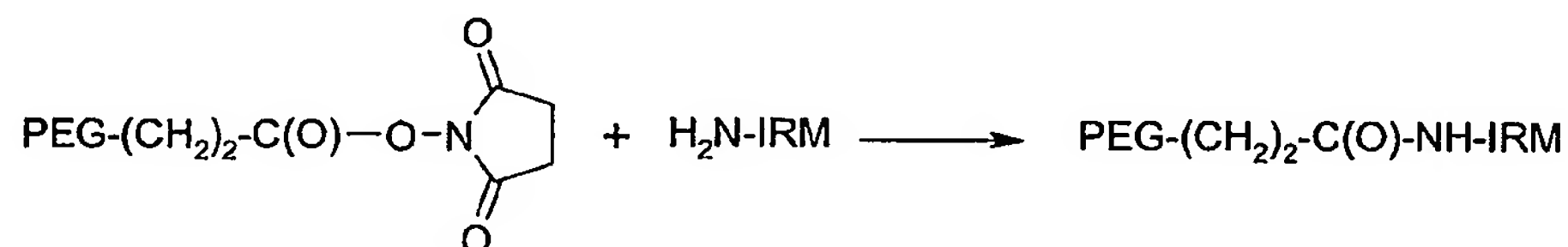
Ammonium hydroxide (20 mL) and *p*-toluenesulfonyl chloride (2.74 g, 14.4 mmol) were added sequentially with rapid stirring to a mixture of the material from Part K in dichloromethane (150 mL), and the reaction was stirred for two hours. The organic layer was then washed with saturated aqueous sodium bicarbonate (2 x) and brine, dried over sodium sulfate, filtered, and concentrated under reduced pressure to provide *tert*-butyl {6-[4-amino-2-ethoxymethyl-1-(2-methanesulfonylamino-2-methylpropyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yloxy]hexyl} carbamate as a red solid.

## Part M

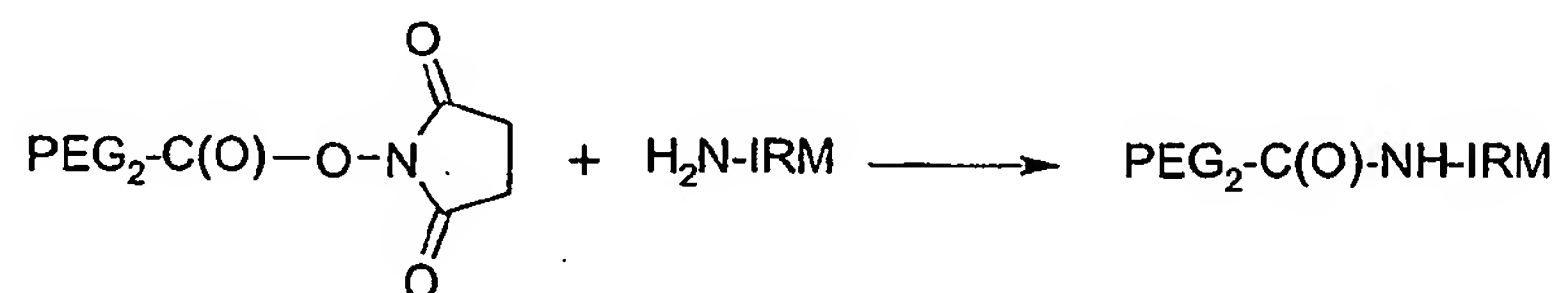
A solution of the material from Part L in hydrochloric acid in ethanol (50 mL of 4.25 M) was heated to reflux and then allowed to cool to ambient temperature. The reaction mixture was purged with nitrogen for approximately 1 hour and then concentrated under reduced pressure. The residue was dissolved in water and then washed with chloroform (x 2). The pH of the aqueous layer was adjusted with ammonium hydroxide and then the aqueous layer was extracted with chloroform (x 3). The combined extracts were washed with brine, dried over sodium sulfate, filtered, and then concentrated under reduced pressure to provide 6.86 g of *N*-{2-[4-amino-7-(6-aminohexyloxy)-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl]-1,1-dimethylethyl}methanesulfonamide as a tan solid.

## Example 1

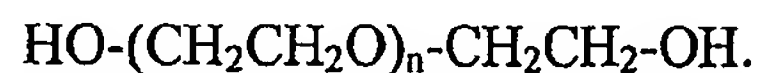
An IRM is covalently attached to a polyethylene glycol polymer by the formation of an amide bond. An IRM containing a pendant amine group is reacted with an activated polyethylene glycol polymer containing an N-hydroxysuccinimidyl ester to form an amide bond as shown below.



The polyethylene glycol polymer may be linear as shown above or branched as shown below.



The polyethylene glycol polymer backbone may be difunctional as shown below.



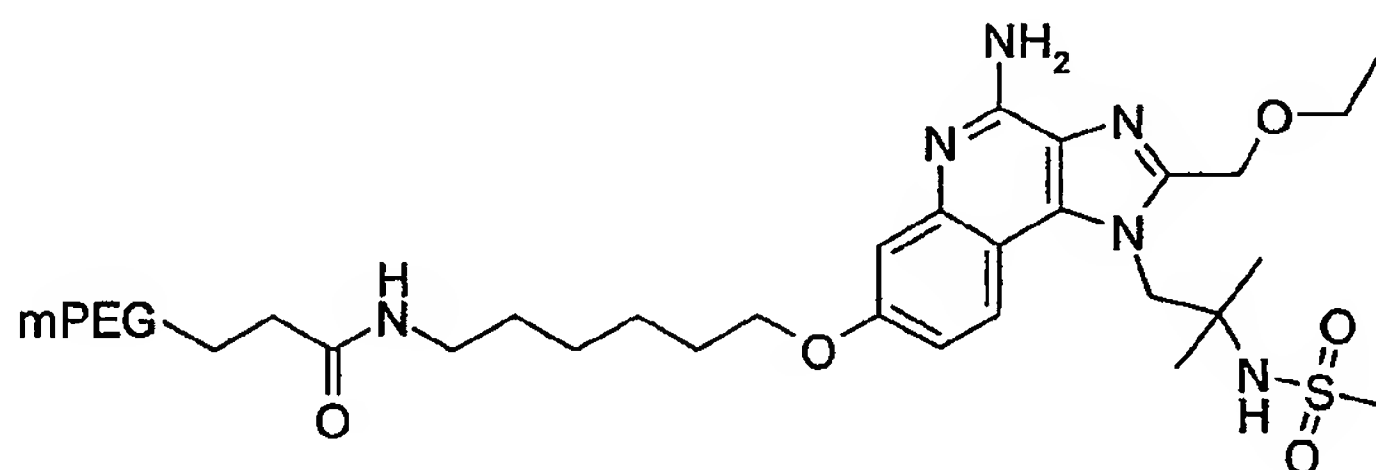
Alternatively, the polyethylene glycol polymer backbone may be capped at one end to provide a monofunctional polymer; for example,



IRMs containing pendant amine groups and methods of making them are known. See, for example, U.S. Pat. Nos. 6,451,810; 6,677,349; 6,660,747; 6,545,016; 6,194,425; and 6,069,149; U.S. Patent Publication No. 2004/0010007; and U.S. Patent Publication  
 5 Nos. 2004/0147543 and 2004/0176367.

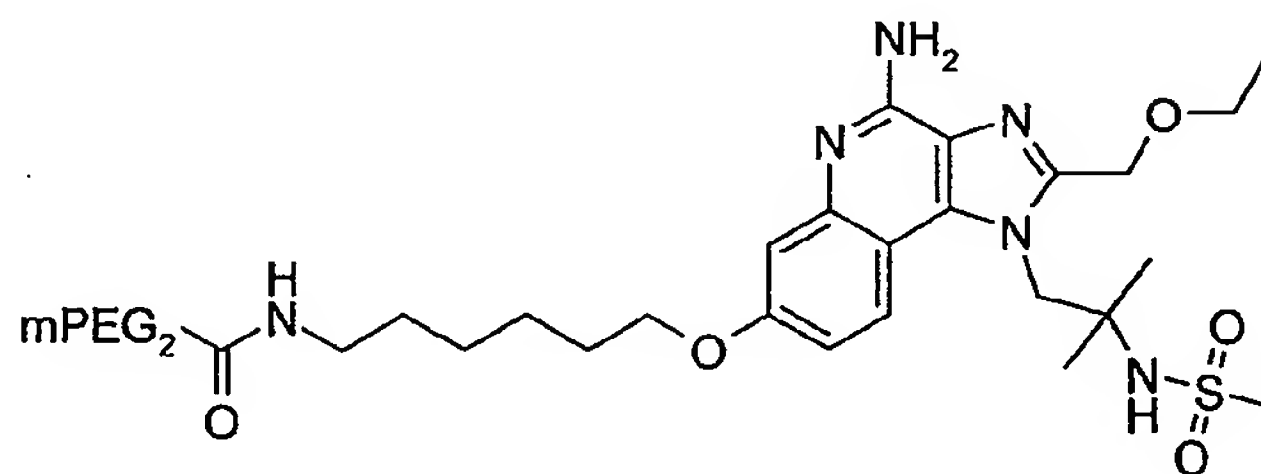
Some activated polyethylene glycol polymers containing N-hydroxysuccinimidyl ester groups are commercially available; for example, those available from Nektar, San Carlos, CA. Others can be prepared using known synthetic methods. See, for example, U.S. Pat. No. 5,583,114 and the references cited therein.

### Example 2



*N*-{2-[4-Amino-7-(6-aminohexyloxy)-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl]-1,1-dimethylethyl}methanesulfonamide is reacted with mPEG-succinimidyl  
 15 propionate having a molecular weight of 2,000 Da (available as mPEG-SPA, MW 2,000 Da, from Nektar). mPEG is a monofunctional polymer having one end capped with a methoxy group.

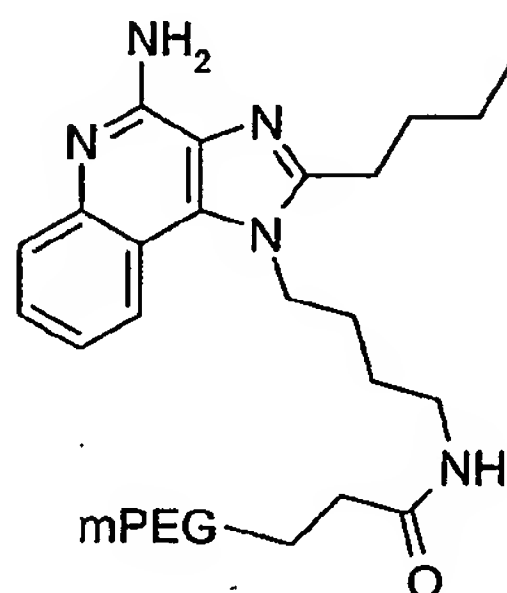
### Example 3



*N*-{2-[4-Amino-7-(6-aminohexyloxy)-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl]-1,1-dimethylethyl}methanesulfonamide is reacted with mPEG<sub>2</sub>-N-

Hydroxysuccinimide having a molecular weight of 40 kDa (available as mPEG<sub>2</sub>-NHS , MW 40 kDa, from Nektar).

## Example 4

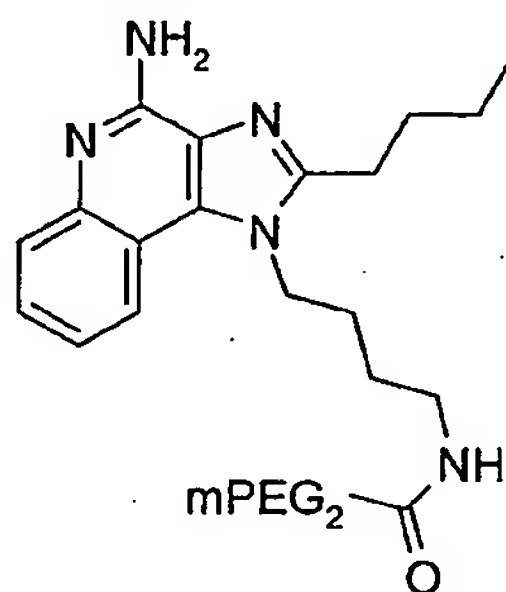


5

1-(4-Aminobutyl)-2-butyl-1*H*-imidazo[4,5-*c*]quinolin-4-amine (which can be prepared according to the methods of U.S. Pat. No. 6,069,149) is reacted with mPEG-succinimidyl propionate having a molecular weight of 2,000 Da (available as mPEG-SPA, MW 2,000 Da, from Nektar).

10

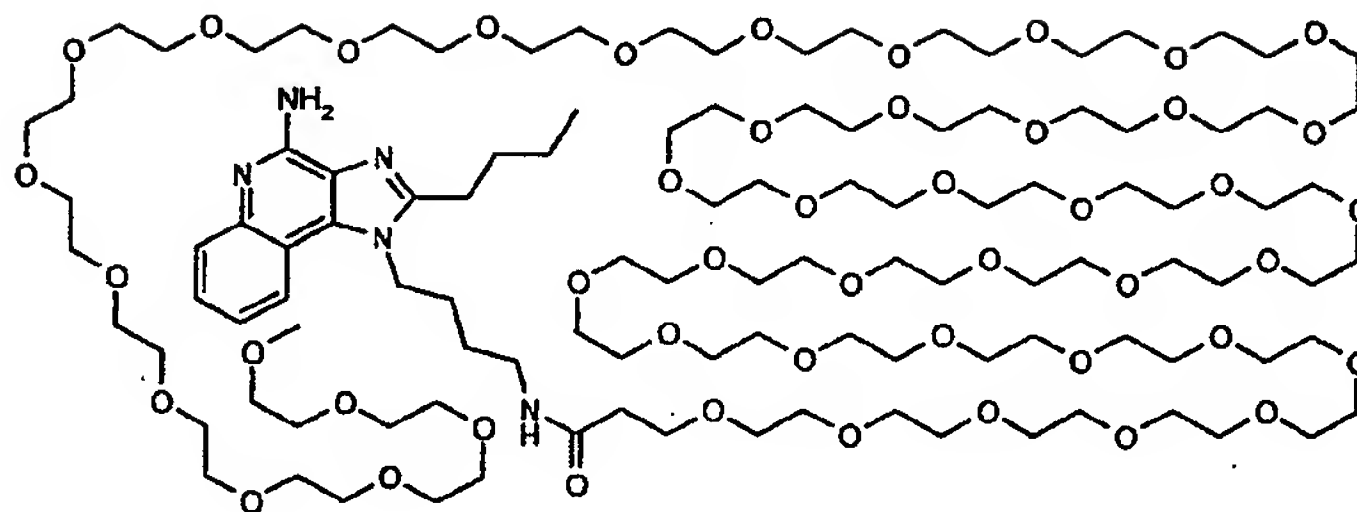
## Example 5



15

1-(4-Aminobutyl)-2-butyl-1*H*-imidazo[4,5-*c*]quinolin-4-amine is reacted with mPEG<sub>2</sub>-N-Hydroxysuccinimide having a molecular weight of 40 kDa (available as mPEG<sub>2</sub>-NHS , MW 40 kDa, from Nektar).

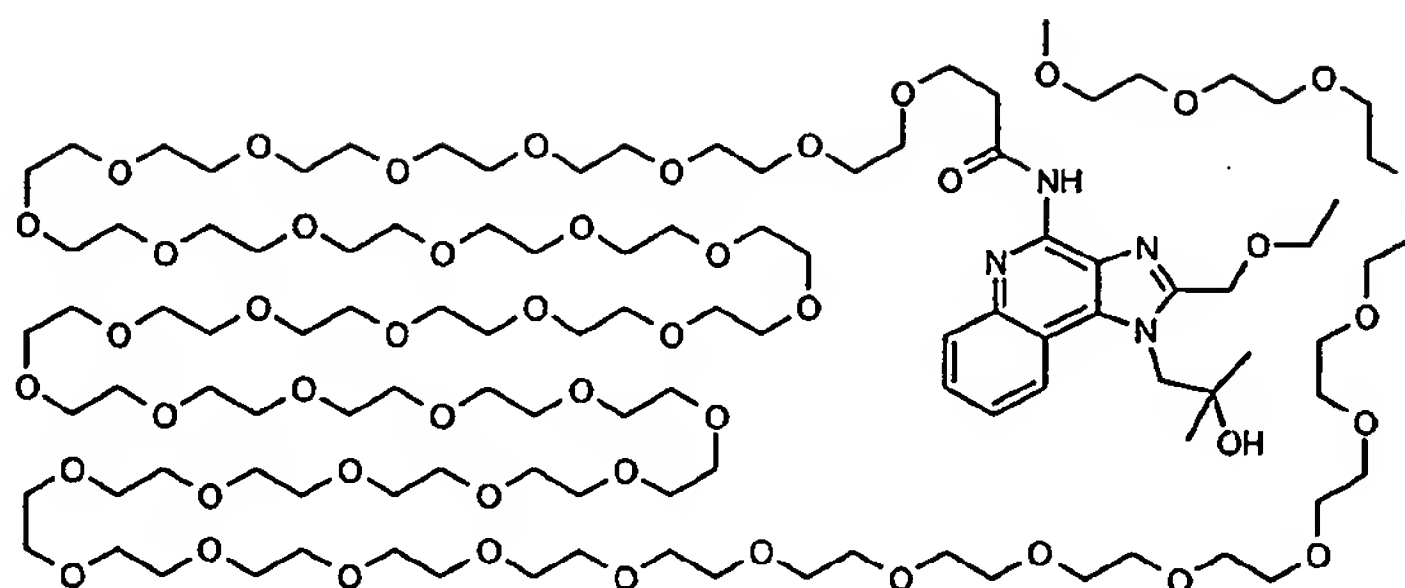
## Example 6



1-(4-Aminobutyl)-2-butyl-1*H*-imidazo[4,5-*c*]quinolin-4-amine (31 mg, 0.10 mmol,  
 5 which can be prepared according to the methods disclosed in U.S. Pat. No. 6,069,149) was  
 dissolved in dichloromethane (5 mL). The solution was stirred under a nitrogen  
 atmosphere and cooled to 0°C. mPEG-succinimidyl propionate having a molecular weight  
 of 2,000 Da (200 mg, available as mPEG-SPA, MW 2,000 Da, from Nektar) was then  
 added and the reaction was stirred overnight. The reaction mixture was then concentrated  
 10 and applied to a silica gel column (2 x 10 cm). Elution with 33% CMA (CMA = 80:18:2  
 v:v:v chloroform/methanol/concentrated ammonium hydroxide) in chloroform gave the  
 desired product as a colorless syrup. Repeated concentration from diethyl ether gave 165  
 mg of product as a white solid, mp 48-49.5°C. Mass spectral analysis showed a bell-  
 shaped distribution of pegylated products centered at about *m/z* 2380. This corresponds to  
 15 45 ethylene oxide units in the PEG chain. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.91 (d, *J* = 8.1  
 Hz, 1H), 7.80 (d, *J* = 8.4 Hz, 1H), 7.49 (m, 1H), 7.31 (m, 1H), 6.72 (m, 1H), 5.39 (s, 2H),  
 4.48 (t, *J* = 7.6 Hz, 2H), 2.91 (t, *J* = 7.8 Hz, 2H), 2.43 (t, *J* = 5.6 Hz, 2H), 1.98-1.75 (m,  
 4H), 1.67 (m, 2H), 1.54 (m, 2H), 1.01 (t, *J* = 7.3 Hz, 3H); QTOF-MS(ESI) *m/z* 2248,  
 2292, 2336, 2380 (C<sub>112</sub>H<sub>211</sub>N<sub>5</sub>O<sub>47</sub>), 2424, 2468, 2512, 2556, 2600, 2644, 2688, 2732.

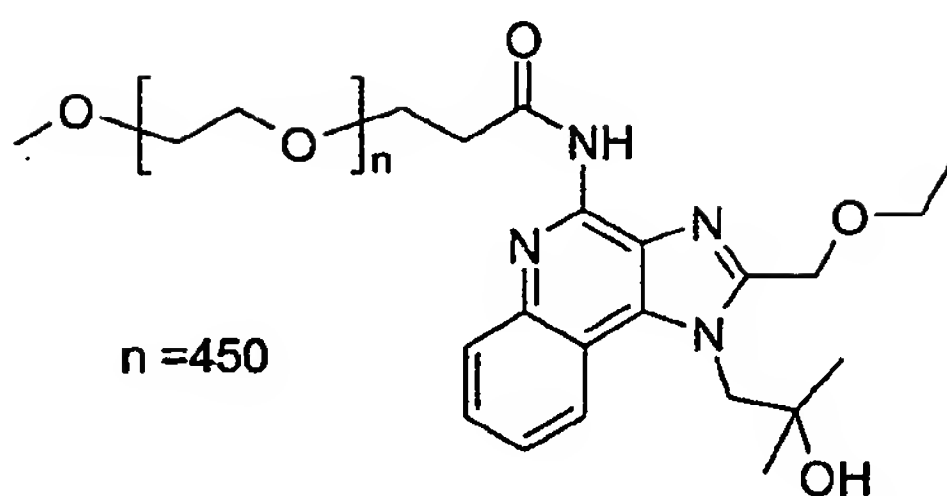
20

## Example 7



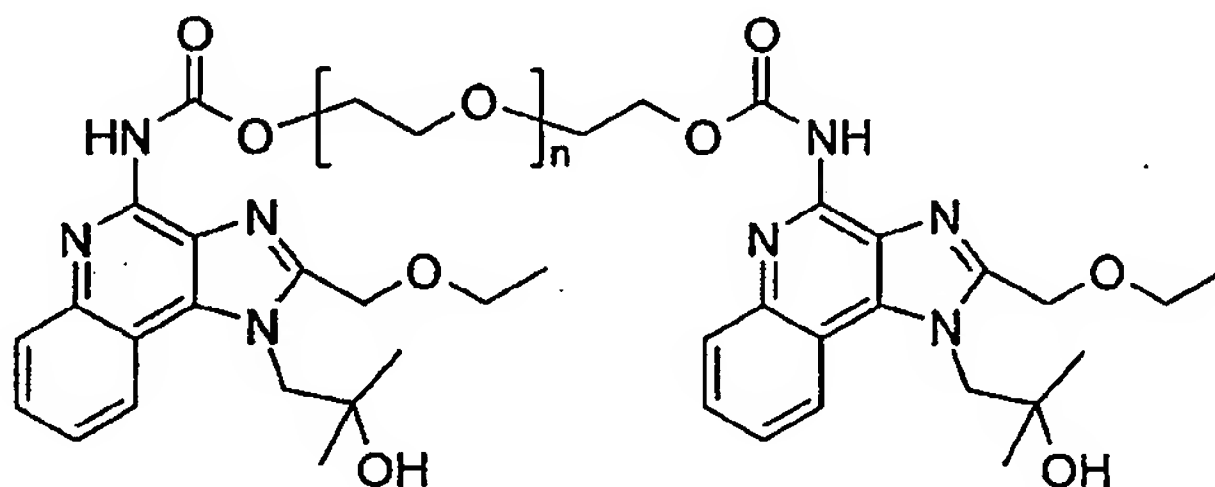
4-Amino-2-ethoxymethyl- $\alpha,\alpha$ -dimethyl-1*H*-imidazo[4,5-*c*]quinoline-1-ethanol  
 5 (resiquimod, 31 mg, 0.10 mmol, which can be prepared as described in Example 99 of  
 U.S. Patent No. 5,389,640) was dissolved in tetrahydrofuran (5 mL). The solution was  
 stirred under a nitrogen atmosphere. mPEG-succinimidyl propionate having a molecular  
 weight of 2,000 Da (231 mg, available as mPEG-SPA, MW 2,000 Da, from Nektar) was  
 added. After 24 hours, 4-dimethylaminopyridine (5 mg) was added and the reaction was  
 10 stirred for 7 days. The reaction mixture was then concentrated and applied to a silica gel  
 column (2.5 x 10 cm). Elution with 3% methanol in chloroform (saturated with  
 ammonium hydroxide), followed by 5% methanol in chloroform (saturated with  
 ammonium hydroxide), and 10% methanol in chloroform (saturated with ammonium  
 hydroxide) gave the desired product as a colorless syrup. Repeated chromatography using  
 15 the same conditions gave pure material. Concentration from diethyl ether gave 110 mg of  
 product as a white solid, mp 51-52°C. Mass spectral analysis showed a bell-shaped  
 distribution of pegylated products centered at about  $m/z$  2383. This corresponds to 45  
 ethylene oxide units in the PEG chain.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  8.30 (d,  $J = 8.2$  Hz,  
 1H), 8.11 (d,  $J = 7.4$  Hz, 1H), 7.67 (m, 1H), 7.56 (t,  $J = 7.3$  Hz, 1H), 4.98 (s, 2H), 4.83 (s,  
 20 2H), 2.50 (t,  $J = 5.5$  Hz, 1H), 1.34 (s, 6H), 1.27 (t,  $J = 7.0$  Hz, 3H). QTOF-MS(ESI)  $m/z$   
 2207, 2251, 2295, 2339, 2383 ( $\text{C}_{111}\text{H}_{208}\text{N}_4\text{O}_{49}$ ), 2427, 2471, 2515, 2559, 2603, 2647,  
 2691, 2735.

## Example 8



Under a nitrogen atmosphere, 4-amino-2-ethoxymethyl- $\alpha,\alpha$ -dimethyl-1H-imidazo[4,5-c]quinoline-1-ethanol (resiquimod, 15 mg, 0.48 mmol) was dissolved in tetrahydrofuran (5 mL). mPEG-succinimidyl propionate having a molecular weight of 20,000 Da (1.00 g, available as mPEG-SPA, MW 20 kDa, from Nektar) was added and the resulting thick suspension was stirred at ambient temperature over night. The reaction mixture was then heated to 50°C and everything went into solution. The solution was heated at 50°C for 7 days and then concentrated under reduced pressure. The residue was dissolved in hot isopropanol (10 mL), the solution was allowed to cool to ambient temperature, and a solid was isolated by filtration. This procedure was repeated to provide about 1.0 g of a white solid.

## Example 9



15

An IRM substituted polyethylene glycol polymer was prepared using the method described in Reaction Scheme III above. A mixture of polyethylene glycol polymer (20 g, 1.0 eq, average  $M_n$  about 35,000) and toluene (80 mL) was heated to 44°C. Phosgene (20% in toluene, 0.71 g, 2.5 eq) was added. Analysis of a small sample of the reaction mixture by infrared spectroscopy showed a band at 1780  $\text{cm}^{-1}$ . The reaction mixture was heated at reflux to drive off the excess phosgene and then cooled back down to 44°C. Triethylamine (121 mg, 2.1 eq) and pentafluorophenol (221 mg, 2.1 eq) were added.

20

Analysis of a small sample of the reaction mixture by infrared spectroscopy showed a band at 1785 cm<sup>-1</sup>. The reaction mixture was concentrated under reduced pressure. The residue was combined with isopropanol (80 mL, dried over molecular sieves) and 4-amino-2-ethoxymethyl- $\alpha,\alpha$ -dimethyl-1*H*-imidazo[4,5-*c*]quinoline-1-ethanol (resiquimod, 367 mg, 2.05 eq). The reaction mixture was heated at reflux for 6 hours and the clear solution was allowed to cool to ambient temperature overnight during which time the reaction mixture solidified. The reaction mixture was warmed until mobile and then poured into isopropanol (about 800 mL). The resulting solid was isolated by filtration and dried to provide 18.9 g of polyethylene glycol polymer end capped with resiquimod.

### Examples 10-12

The IRM compounds used in the Examples provided below are identified in Table 1.

Table 1

Compound	Chemical Name	Reference
IRM 1	4-amino- $\alpha,\alpha$ -dimethyl-2-ethoxymethyl-1 <i>H</i> -imidazo[4,5- <i>c</i> ]quinolin-1-ethanol	U.S. Pat. No. 5,389,640 Example 99
IRM 2	N-[4-(4-Amino-2-butyl-1 <i>H</i> -imidazo[4,5- <i>c</i> ]quinolin-1-yl)butyl]acetamide	U.S. Pat. No. 6,451,810#

# This compound is not specifically exemplified but can be readily prepared using the synthetic methods disclosed in the cited reference.

### Example 10

An in vitro human blood cell system is used to assess cytokine induction. Activity is based on the measurement of interferon ( $\alpha$ ) and tumor necrosis factor ( $\alpha$ ) (IFN- $\alpha$  and TNF- $\alpha$ , respectively) secreted into culture media as described by Testerman et. al. in "Cytokine Induction by the Immunomodulators Imiquimod and S-27609," *Journal of Leukocyte Biology*, 58, 365-372 (September, 1995).

### Blood Cell Preparation for Culture

Whole blood from healthy human donors is collected by venipuncture into vacutainer tubes or syringes containing EDTA. Peripheral blood mononuclear cells (PBMC) are separated from whole blood by density gradient centrifugation using  
5 HISTOPAQUE-1077 (Sigma, St. Louis, MO) or Ficoll-Paque Plus (Amersham Biosciences Piscataway, NJ). Blood is diluted 1:1 with Dulbecco's Phosphate Buffered Saline (DPBS) or Hank's Balanced Salts Solution (HBSS). Alternately, whole blood is placed in Accuspin (Sigma) or LeucoSep (Greiner Bio-One, Inc., Longwood, FL) centrifuge frit tubes containing density gradient medium. The PBMC layer is collected  
10 and washed twice with DPBS or HBSS and re-suspended at  $4 \times 10^6$  cells/mL in RPMI complete. The PBMC suspension is added to 96 well flat bottom sterile tissue culture plates containing an equal volume of RPMI complete media containing test compound.

### Compound Preparation

15 The compounds are solubilized in dimethyl sulfoxide (DMSO). The DMSO concentration should not exceed a final concentration of 1% for addition to the culture wells. The compounds are generally tested at concentrations ranging from 30-0.014  $\mu$ M. Controls include cell samples with media only, cell samples with DMSO only (no compound), and cell samples with reference compound.

20

### Incubation

The solution of test compound is added at 60  $\mu$ M to the first well containing RPMI complete and serial 3 fold dilutions are made in the wells. The PBMC suspension is then added to the wells in an equal volume, bringing the test compound concentrations to the  
25 desired range (usually 30-0.014  $\mu$ M). The final concentration of PBMC suspension is  $2 \times 10^6$  cells/mL. The plates are covered with sterile plastic lids, mixed gently and then incubated for 18 to 24 hours at 37°C in a 5% carbon dioxide atmosphere.

### Separation

30 Following incubation the plates are centrifuged for 10 minutes at 1000 rpm (approximately 200 x g) at 4°C. The cell-free culture supernatant is removed and transferred to sterile polypropylene tubes. Samples are maintained at -30 to -70°C until

analysis. The samples are analyzed for IFN- $\alpha$  by ELISA and for TNF- $\alpha$  by IGEN/BioVeris Assay.

#### Interferon ( $\alpha$ ) and Tumor Necrosis Factor ( $\alpha$ ) Analysis

5 IFN- $\alpha$  concentration is determined with a human multi-subtype colorimetric sandwich ELISA (Catalog Number 41105) from PBL Biomedical Laboratories, Piscataway, NJ. Results are expressed in pg/mL.

The TNF- $\alpha$  concentration is determined by ORIGEN M-Series Immunoassay and read on an IGEN M-8 analyzer from BioVeris Corporation, formerly known as IGEN  
10 International, Gaithersburg, MD. The immunoassay uses a human TNF- $\alpha$  capture and detection antibody pair (Catalog Numbers AHC3419 and AHC3712) from Biosource International, Camarillo, CA. Results are expressed in pg/mL.

#### Assay Data and Analysis

15 In total, the data output of the assay consists of concentration values of TNF- $\alpha$  and IFN- $\alpha$  (y-axis) as a function of compound concentration (x-axis).

Analysis of the data has two steps. First, the greater of the mean DMSO (DMSO control wells) or the experimental background (usually 20 pg/mL for IFN- $\alpha$  and 40 pg/mL for TNF- $\alpha$ ) is subtracted from each reading. If any negative values result from  
20 background subtraction, the reading is reported as " $\ast$ ", and is noted as not reliably detectable. In subsequent calculations and statistics, " $\ast$ " is treated as a zero. Second, all background subtracted values are multiplied by a single adjustment ratio to decrease experiment to experiment variability. The adjustment ratio is the area of the reference compound in the new experiment divided by the expected area of  
25 the reference compound based on the past 61 experiments (unadjusted readings). This results in the scaling of the reading (y-axis) for the new data without changing the shape of the dose-response curve. The reference compound used is 2-[4-amino-2-ethoxymethyl-6,7,8,9-tetrahydro- $\alpha,\alpha$ -dimethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl]ethanol hydrate (U.S. Patent No. 5,352,784; Example 91) and the expected area is the sum of the median dose  
30 values from the past 61 experiments.

The minimum effective concentration is calculated based on the background-subtracted, reference-adjusted results for a given experiment and compound. The

minimum effective concentration ( $\mu$ molar) is the lowest of the tested compound concentrations that induces a response over a fixed cytokine concentration for the tested cytokine (usually 20 pg/mL for IFN- $\alpha$  and 40 pg/mL for TNF- $\alpha$ ). The maximal response (pg/mL) is the maximal response attained in the dose response curve. Results are shown in Table 2.

Table 2

Compound	Minimum Effective Concentration (mM)	
	IFN- $\alpha$	TNF
IRM 1	0.12	0.37
IRM 2	0.014	1.11
Example 6	30	>30
Example 7	3.33	30

#### Example 11

Example 7 and Example 8 were prepared at 0.1 and 1.0 mg/ml, respectively, in either citrate buffered saline at pH 4 or phosphate buffered saline at pH 7.4. Samples were placed in a thermostated autosampler with the temperature controlled at 37°C. Samples were injected periodically over the course of the experiment and the % of IRM1 liberated was measured by an HPLC system equipped with a thermostatted autosampler set at 37°C and a Zorbax SB C18, (3.0  $\times$  150 mm), 3.5  $\mu$ m particle size column with a column temperature of 40°C. Samples were eluted with a mobile phase of 1% acetic acid in water and methanol. The mobile phase was run at a ratio of 55:45 of 1% acetic acid in water to methanol for five minutes, gradient to 5:95 for ten minutes, held at 5:95 for five minutes, gradient to 55:45 in less than a minute, and held at 55:45 for ten minutes. All HPLC runs were set at a flow rate of 0.5 mL/min, 20  $\mu$ L injection volume, and a 254 nm UV detection wavelength. The % IRM1 was determined by normalizing the IRM1 peak area by the total peak area of the chromatogram. Results for Example 7 and Example 8 are shown in Tables 3 and 4, respectively.

Table 3

Citrate Buffered Saline, pH 4, 37°C		Phosphate Buffered Saline, pH 7.4, 37°C	
Time (hr)	% IRM1	Time (hr)	% IRM1
0	2.9%	1	1.3%
6	5.7%	5	1.5%
10	7.4%	10	1.7%
13	9.4%	13	1.8%
17	10.6%	18	1.9%
20	12.1%	20	2.1%
23	13.0%	23	2.1%
28	16.5%	27	2.3%
30	17.1%	30	2.4%

Table 4

Citrate Buffered Saline, pH 4, 37°C		Phosphate Buffered Saline, pH 7.4, 37°C	
Time (hr)	% IRM1	Time (hr)	% IRM1
0	NM	0	NM
6	6.2%	7	3.6%
10	7.7%	11	3.7%
13	9.2%	14	3.8%
17	11.0%	18	4.0%
20	12.6%	21	4.1%
23	14.1%	24	4.2%
28	16.0%	29	4.4%
31	17.7%	32	4.5%
NM = Not Measured			

## Example 12

The solubility of IRM2 and the IRM-polymer complex exemplified in Example 6 was determined in normal saline and phosphate buffered saline (PBS) at pH 7.4. Each compound was added to each medium until saturation had been reached. Vials containing the saturated solutions were capped and placed into a shaking water bath at 25°C. After 7 days the saturated solutions were filtered and analyzed for compound content on an HPLC using a Zorbax Bonus-RP 150 x 4.6 mm 5 µm particle size column. IRM2 was eluted with a 25:75 ratio of 0.05% trifluoro-acetic acid (TFA) in Acetonitrile to 0.1% TFA in water. Example 6 was eluted with a 10:90 ratio of 0.05% TFA in Acetonitrile to 0.1% TFA in water for three minutes, gradient to a 75:25 ratio of 0.05% TFA in Acetonitrile to 0.1% TFA in water for seven minutes and held at the 75:25 ratio for eight minutes. All HPLC runs were set at a flow rate of 1 mL/min, 20 µL injection volume, and a 254 nm UV detection wavelength. Quantitation was performed against external standards. Results are shown in Table 5 expressed in millimolar (mM) and solubility fold increase of Example 6 over IRM2.

Table 5

Aqueous System	Solubility		
	IRM2 (mM)	Example 6 (mM)	Fold Increase
Saline	0.04	5.97	142.50
Phosphate Buffered Saline, pH 7.4	0.07	5.59	75.97

20

The complete disclosures of the patents, patent documents and publications cited herein are incorporated by reference in their entirety as if each were individually incorporated. In case of conflict, the present specification, including definitions, shall control. Various modifications and alterations to this invention will become apparent to

those skilled in the art without departing from the scope and spirit of this invention. Illustrative embodiments and examples are provided as examples only and are not intended to limit the scope of the present invention. The scope of the invention is limited only by the claims set forth as follows.

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What is claimed is:

1. A method of delivering one or more IRM compounds to a tissue in a subject, the method comprising administering an IRM preparation to the subject, wherein the IRM preparation comprises a soluble IRM-polymer complex comprising one or more IRM compounds attached to a polymer.
2. A method of delivering one or more IRM compounds to a tissue in a subject, the method comprising administering an IRM preparation to the subject, wherein the IRM preparation comprises a soluble IRM-polymer complex comprising one or more IRM compounds attached to a soluble polymer comprising alkylene oxide moieties, wherein the IRM-polymer complex has a molecular weight of 1 kDa to 500 kDa.
3. The method of claim 1 or claim 2 wherein the soluble IRM-polymer complex has a solubility of at least 1 microgram per milliliter in water under physiological conditions.
4. The method of claim 1 or claim 2 wherein the soluble IRM-polymer complex has a solubility of at least 0.1 microgram per milliliter in water under physiological conditions.
5. The method of claim 4 wherein the soluble IRM-polymer complex has a solubility of at least 0.1 and less than 1 microgram per milliliter in water under physiological conditions.
6. The method of any one of claims 1 through 5 wherein one or more IRM compounds are covalently attached to a soluble polymer.
7. The method of claim 2 or claim 6 wherein the soluble polymer has a molecular weight of 1 kDa to 500 kDa.
8. The method of claim 7 wherein the soluble polymer has a molecular weight of 1 kDa to 200 kDa.

9. The method of claim 2 or any one of claims 6 through 8 wherein the soluble polymer has a solubility of at least 1 microgram per milliliter in water under physiological conditions.
- 5 10. The method of claim 2 or any one of claims 6 through 8 wherein the soluble polymer has a solubility of at least 0.1 microgram per milliliter in water under physiological conditions.
- 10 11. The method of claim 10 wherein the soluble polymer has a solubility of at least 0.1 and less than 1 microgram per milliliter in water under physiological conditions.
12. The method of any one of claims 1 through 11 wherein the tissue is a localized tissue region.
- 15 13. The method of claim 12 wherein the localized tissue region is a particular organ subject to a disease that is treatable using the IRM compound.
14. The method of claim 13 wherein the localized tissue region is a tumor.
- 20 15. The method of claim 14 wherein the localized tissue region is a breast cancer tumor, a stomach cancer tumor, a lung cancer tumor, a head or neck cancer tumor, a colorectal cancer tumor, a renal cell carcinoma tumor, a pancreatic cancer tumor, a basal cell carcinoma tumor, a cervical cancer tumor, a melanoma cancer tumor, a prostate cancer tumor, an ovarian cancer tumor, or a bladder cancer tumor.
- 25 16. The method of claim 12 wherein the localized tissue region is a viral infected lesion or organ.
- 30 17. The method of claim 1 or any one of claims 3 through 16 except as dependent on claim 2 wherein the polymer comprises alkylene oxide moieties.

18. The method of any one of claims 1 through 17 wherein the IRM is an agonist of at least one TLR selected from the group consisting of TLR7 and TLR8.
19. The method of claim 18 wherein the IRM is a TLR agonist of TLR 7.
20. The method of claim 18 wherein the IRM is a TLR agonist of TLR 8.
21. The method of claim 18 wherein the IRM is a TLR agonist of both TLR 7 and 8.
22. The method of claim 1 or any one of claims 3 through 21 except as dependent on claim 2 wherein the soluble IRM-polymer complex has a molecular weight of 1 kDa to 500 kDa.
23. The method of any one of claims 1 through 22 wherein the IRM-polymer complex has a molecular weight of 1 kDa to 200 kDa.
24. The method of claim 23 wherein the IRM-polymer complex has a molecular weight of 1 kDa to 100 kDa.
25. The method of claim 24 wherein the IRM-polymer complex has a molecular weight of 30 kDa to 100 kDa.
26. The method of any one of claims 1 through 25 wherein the IRM is a small molecule immune response modifier.
27. The method of any one of claims 1 through 25 wherein the IRM compound is selected from the group consisting of imidazoquinoline amines; tetrahydroimidazoquinoline amines; and imidazopyridine amines; 1,2-bridged imidazoquinoline amines; 6,7-fused cycloalkylimidazopyridine amines; imidazonaphthyridine amines; tetrahydroimidazonaphthyridine amines; oxazoloquinoline amines; thiazoloquinoline amines; oxazolopyridine amines; thiazolopyridine amines; oxazolonaphthyridine amines; thiazolonaphthyridine amines; 1*H*-imidazo dimers fused to

pyridine amines, quinoline amines, tetrahydroquinoline amines, naphthyridine amines, or tetrahydronaphthyridine amines; and combinations thereof.

28. The method of any one of claims 1 through 25 wherein the IRM compound is  
5 selected from the group consisting of purines, imidazoquinoline amides, benzimidazoles, 1*H*-imidazopyridines, adenines, and derivatives thereof.

29. The method of any one of claims 1 through 25 wherein the IRM compound  
10 comprises a 2-aminopyridine fused to a five-membered nitrogen-containing heterocyclic ring.

30. The method of any one of claims 1 through 25 wherein the IRM compound  
15 comprises a 4-aminopyrimidine fused to a five-membered nitrogen containing heterocyclic ring.

31. The method of any one of claims 1 through 30 wherein the IRM preparation  
further comprises one or more additional active ingredients.

32. The method of claim 1 or any one of claims 3 through 31 except as dependent on  
20 claim 2 wherein the polymer is a soluble polymer selected from the group consisting of poly(alkylene glycols), poly(olefinic alcohols), polyvinylpyrrolidones, poly(hydroxyalkylmethacrylamides), poly(hydroxyalkylmethacrylates), polyvinyl alcohols, polyoxazolines, poly(acrylic acids), polyacrylamides, polyglutamates, polylysines, polysaccharides, and combinations thereof.

33. A soluble IRM-polymer complex comprising one or more IRM compounds  
25 attached to an alkylene oxide-containing polymer.

34. A soluble IRM-polymer complex comprising one or more IRM compounds  
30 attached to a polymer, wherein the polymer prior to attachment of the one or more IRM compounds has a solubility in water of at least 0.1 microgram per milliliter under physiological conditions.

35. The soluble IRM-polymer complex of claim 33 wherein the polymer prior to attachment of the one or more IRM compounds has a solubility in water of at least 0.1 microgram per milliliter under physiological conditions.

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36. The soluble IRM-polymer complex of claim 33 or claim 34 wherein the polymer prior to attachment of the one or more IRM compounds has a solubility of at least 1 microgram per milliliter in water under physiological conditions.

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37. The soluble IRM-polymer complex of claim 34 or claim 35 wherein the polymer prior to attachment of the one or more IRM compounds has a solubility of at least 0.1 and less than 1 microgram per milliliter in water under physiological conditions.

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38. The soluble IRM-polymer complex of any one of claims 33 through 36 wherein the soluble IRM-polymer complex has a solubility of at least 1 microgram per milliliter in water under physiological conditions.

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39. The soluble IRM-polymer complex of claim 38 wherein the soluble IRM-polymer complex has a solubility of at least 10 micrograms per milliliter in water under physiological conditions.

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40. The soluble IRM-polymer complex of any one of claims 33 through 36 wherein the soluble IRM-polymer complex has a solubility of at least 0.1 microgram per milliliter in water under physiological conditions.

41. The soluble IRM-polymer complex of claim 40 wherein the soluble IRM-polymer complex has a solubility of at least 0.1 and less than 1 microgram per milliliter in water under physiological conditions.

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42. The soluble IRM-polymer complex of any one of claims 33 through 41 wherein the IRM-polymer complex has a molecular weight of 1 kDa to 500 kDa.

43. The soluble IRM-polymer complex of any one of claims 33 through 41 wherein the IRM-polymer complex has a molecular weight of 1 kDa to 200 kDa.
44. The soluble IRM-polymer complex of claim 43 wherein the IRM-polymer complex has a molecular weight of 1 kDa to 100 kDa.
45. The soluble IRM-polymer complex of claim 43 wherein the IRM-polymer complex has a molecular weight of 20 kDa to 200 kDa.
46. The soluble IRM-polymer complex of claim 45 wherein the IRM-polymer complex has a molecular weight of 30 kDa to 100 kDa.
47. The soluble IRM-polymer complex of any one of claims 33 through 46 wherein the one or more IRM compounds are covalently attached to an alkylene oxide-containing polymer.
48. The soluble IRM-polymer complex of claim 34 or any one of claims 36 through 46 except as dependent on claim 33 wherein the soluble polymer is selected from the group consisting of poly(alkylene glycols), poly(olefinic alcohols), polyvinylpyrrolidones, poly(hydroxyalkylmethacrylamides), poly(hydroxyalkylmethacrylates), polyvinyl alcohols, polyoxazolines, poly(acrylic acids), polyacrylamides, polyglutamates, polylysines, polysaccharides and combinations thereof.
49. An IRM preparation comprising any one of the IRM-polymer complexes of claims 33 through 48.
50. The IRM preparation of claim 49 further comprising one or more additional active agents.
51. The IRM preparation of claim 50 wherein the additional active agents are attached to the alkylene oxide-containing polymer.

52. The IRM preparation of claim 49 further comprising one or more IRM compounds that are not attached to the alkylene oxide-containing polymer.